A REVIEW ON MANAGEMENT OF DYSLIPIDEMIA

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ABSTRACT

Dyslipidemia is one of the main risk factors in the development of cardiovascular diseases. Currently, there are different alternatives available (amongst which statins, resins, fibric acid derivatives, nicotinic acid fish oils, dietary supplements etc.), to optimize the treatment of patients at high or very high cardiovascular risk. Despite this, the percentage of patients that achieve good lipid control is low. The causes of the mismatch with proposed objectives include lack of patient adherence and therapeutic inertia. Lifestyle changes (improved diet and increased physical activity) are effective TG lowering measures. Pharmacological treatment usually starts with statins, resins, fibric acid derivatives, niacin, fish oil, dietary supplements although associated hypercholesterolemia reductions are typically modest. Fibrates are currently the drugs of choice for hypetriglyceridemia frequently in combination with statins. Niacin and omega-3 fatty acids improve control of triglyceride levels when the above measures are inadequately effect.

This review uses available evidence and the latest clinical guides as a basis to assess the pharmacological treatment of dyslipidemia in patients with a background of arteriosclerotic vascular disease, diabetes, chronic kidney disease, hypothyroidism, cardiovascular risk at ≥5% calculated by SCORE and familial hypercholesterolemia. The treatment of hypercholesterolemia is also reviewed along with the special consideration. The global assessment of cardiovascular risk is of high priority to adapt treatment to the specific objectives of the c-LDL for each risk category.

Keywords: Dyslipidemia, statins, Resins, fibrates- fenofibrate, neutraceticals, niacin, fish oils, side -effect, hypercholesterolemia, diabetes, hypertension, cardiovascular, LDL-c
INTRODUCTION

The role of cholesterol in a pathogenesis of atherosclerotic heart disease remained controversial until surprisingly recently. It mean increase level plasma concentration that role of important constituent of the plaque furnished landmark clues in the case against cholesterol in the pathogenesis of cardiovascular diseases. Early mortality due to communicable diseases subsided, chronic diseases especially atherosclerosis, become most important causes of mortality and disability. The important of serum(or plasma) cholesterol emerged not only from the large epidemiological studies conducted after world war second but also from the large body of epidemiological data that include seven country study, the ni-hon-san study, the Northwick park study, and, more recently, the prospective cardiovascular munster (PROCAM) study. Analytical methodologies, especially in the use of ultracentrifuge( which allow separation of plasma lipoproteins),provided important data on the relationship between low density lipoproteins(LDL) and possible very low density lipoproteins(VLDL)and the coronary artery disease. The role of high density lipoproteins(HDL) as a protective factor are emerged. Data regarding the role of the diet in cardiovascular diseases only added to confusion. The seven country study provided compelling data plasma cholesterol levels corrected much more with saturated fat intake than with dietary cholesterol. The cardiovascular disease (CVD) is the major cause of death in developed country and the now it is increasing of the world problem and account CVD take the lives of 17.7 million people every year, 31% of all global deaths, triggering these diseases are tobacco, smoking, unhealthy diet, lack of physical activity. >75% CVD deaths occur in low-income and middle-income country. 80% of all CVD deaths are due to heart attacks and strokes. Cardiovascular (CVD) is 3rd commonest death in the world.

TREATMENT OF DYSLIPIDEMIA

Specific treatment:


Modifications of lifestyle:

Physical inactivity, obesity, diet rich in fats, saturated fats, alcohol intake. Reduction of dose, some drugs if patient who has significant suffer from dyslipidemia for examples: corticosteroids, immunosuppressive agents, retinoids, highly active antiretroviral therapy (HAART), thiazides, beta-adrenergic blockers. Modification the lifestyle of the patient with severe hypertriglyceridemia often is
associated with significant reduction in plasma TG level. Patients who drink alcohol should be encouraged to decrease or preferably eliminate their intake. Patients with severe hypertriglyceridemia often benefit from a formal consultation with a dietician intimately familiar with counseling patients on the dietary management of high TGs. Dietary fat intake should be restricted to reduce the formation of chylomicrons in the intestine. The excessive intake of simple carbohydrates should be discouraged because insulin drives TG production in the liver. Aerobic exercise and even increase regular physical activity can have a positive effect in reducing TG level and should be strongly encouraged for patients who overweight, weight loss, and can help to reduce TG levels.

The diet should have three objectives: [1] It should to allow the patient to reach maintain ideal body weight; [2] It should provide a well balanced diet with fruits, vegetables and grains; [3] It should be restricted in saturated fats and refined carbohydrate. The source of dietitian prove valuable in this regard. Present guidelines recommend a diet in which protein intake present 15-20% of the calories and fats represent 25 to 30% (with only one third of saturated fats). The remaining calories are obtained from carbohydrates. Cholesterol intake is limited to less than 300mg/day.

Resins:

The bile acid-binding resins act to interrupt the enterohepatic circulation of bile acids by inhibiting their reabsorption in the intestine (bile acids that contain cholesterol are more than 90% reabsorbed through this pathway). Their main indication is as adjunctive therapy in the patient with severe hypercholesterolemia due to increase LDL-C because bile acid binding resins are not absorbed systemically (they remain in the intestine and are eliminated in the stool). They are considered safe in children. Cholestramine is used 4gm of anhydrous resin. Colestipol used 5gm unit doses. The side effects are gastrointestinal with constipation, a sensation of fullness, and gastrointestinal discomfort.

HMG Coa REDUCTASE INHIBITORS (STATINS):

Therapeutic doses reduce CH synthesis by 20-50%. This results in compensatory increase in LDL receptor expression on liver cells that increased receptor mediated uptake and catabolism of IDL and LDL.

Comparison of two lipid-lowering strategies in patients with CAD:

Atorvastatin at different doses (80mg vs. 10mg) and concludes that treatment with atorvastatin 80mg/day reduces the incidence of myocardial infarction and both fatal and non-fatal stroke in comparison with the administration of 10mg/day which reduces LDL-c to a lesser extent. Moreover, there is evidence on intensive therapy with rosuvastatin achieving further reduction of LDL-c in comparison with conventional treatment and the regression of aortic atheromatosis. Moreover, at their maximum recommended doses
simvastatin (80mg) causes 45 to 50% reduction, while atorvastatin (80mg) and rosuvastatin (40mg) can reduce LDL-CH by upto 55%. The ceiling effect of lovastatin and pravastatin is 30 to 40%LDL-CH reduction. All statins produce peak LDL-CH lowering after 1-2 weeks therapy. With lovastatin a mean reduction of LDL-CH by 25% at 20mg/d, 32% at 40mg /d and 40% at 80mg/day.

**Side Effect Of Statins:** Muscles aches are the commonest 10% side effect. Dyspepsia, headache, fatigue, joint pain, myopathy, severe myopathy even rhabdomyolysis. Myopathy is more common when nicotinic acid/gemfibrozil or CYP3A4 inhibitor- ketoconazole/erythromycin/cyclosporins/HIV protease inhibitor is given concurrently, grapefruit juice, amiodarone, and several others.  

**Fish Oil (Omega 3 Fatty Acids):**

Fish oils are rich in polyunsaturated fatty acids with the first double bond in omega-3 positions, such as eicosapentaenoic acid or docosahexaenoic acid. They fatty acids have been found in lower plasma triglyceride levels to have antithrombotic and perhaps anti-inflammatory properties. Although they have been used in the treatment of hypertriglyceridemia. Tablet and in doses of 3-4 g/day are effective at lowering fasting TG level.

**Nicotinic Acids (Niacin):**

Treatment of dyslipidemia and is particularly effective in increasing HDL-C and lowering triglyceride level. The effect of niacin on LDL-C is more modest. It is a B-complex vitamin that has been used as a lipid-modifying agent for more than five decades. Niacin suppresses lipolysis in the adipocyte through its effects on the niacin receptors. Effective doses of niacin are in the range of 3000mg/day. Aspirin may ameliorate niacin induced skin flushing. Niacin decreases the hepatic secretion of VLDL from the liver and decrease FFA mobilization for the periphery. Although niacin has been shown in the long term follow up of the coronary drug project to decrease mortality at 15 years.

**Side Effect Of Niacin:** Flushing, hyperuricemia, hyperglycemia, hepatotoxicity, acanthosis nigricans, and gastritis.

**FIBRIC ACID DERIVATIVES (Fibrates):**

**Fenofibrate:** is used to treat hypertriglyceridemia and combine with hyperlipoproteinemia. The dose is 200mg/day and new formulation is available to vary dose from 67mg (especially in renal failure) to the 200mg/day. The fundamental action of fenofibrate is the promotion of apo A I and II synthesis in the liver, which represent the main HDL-C apoproteins. Fenofibrate modifies HDL and the reverse cholesterol transport pathway through several mechanisms. Specifically, fenofibrate is able to increase pre-β1-HDL-C levels in patients with the metabolic syndrome, reduce total plasma cholesteryl ester transfer protein
activity,\textsuperscript{16,17} induce the activity of adenosine triphosphate-binding cassette transporter (ABCA1,\textsuperscript{18,19} member 1 of the human transporter subfamily ABCA), also known as the cholesterol efflux regulatory protein (CERP), and induce hepatic lipase activity.\textsuperscript{20} Some recent clinical reports have suggested that HDL-C levels may be paradoxically decreased after fenofibrate treatment.\textsuperscript{21,22} This appears to occur mainly in patients with combined fibrate plus statin therapy and possibly in those with low baseline HDL-C. A survey of 581 patients treated with the combination for 1 year or longer indicated that paradoxical HDL-C reductions are a relatively uncommon phenomenon.\textsuperscript{23} Approximately 15% of patients showed modest reduction in HDL-C levels. These reductions in HDL-C occurred mainly in individuals with significant HDL-C elevations (ie, .50 mg/dL, 1.3 mmol/L) and almost never in patients with low HDL-C. There was no impact of a previous diagnosis of diabetes or hypertension on the HDL-C changes.\textsuperscript{24} In addition, fibrates have been shown to decrease cholesterol synthesis by inhibiting hydroxymethylglutamylcoenzyme A reductase and to increase cholesterol excretion in the bile pool.\textsuperscript{25-27}

**Side effect of fenofibrate:** myalgia, hepatitis, rashes, cholelithiasis and rare rhabdomyolysis.

**Gemfibrozil:**

This is fibric acid derivative effectively lowers plasma TG level by enhancing breakdown and suppressing hepatic synthesis of TGs. Besides high efficacy in type 3 hyperlipoproteinemia, gemfibrozil has shown action in subjects with raised blood CH in addition. Helsinki heart study men without known CAD treated with gemfibrozil had a 34% reduction in fatal and nonfatal MI.

**Side effect of gemfibrozil:** epigastric distress, loose motion, skin rashes, body ache, eosinophilia, impotence, headache, blurred vision. Myopathy is uncommon.

**Bezafibrate:**

This second generation fibric acid derivative is an alternative to gemfibrozil in mixed hyperlipidemia (type 3, 4 and 5) though it has been indicated in hypercholesterolaemia (type 2). It is inferior to statins and resins. Bezafibrate has not shown propensity to increase LDL-CH in hypertriglyceridaemic patients and appear to have greater LDL-CH lowering action than gemfibrozil.

**Side effect and adverse effect of bezafibrate:** similar to other fibrates

Main side effect are gastrointestinal upset, myalgia, rashes. Dose reduction is needed in elderly and in renal failure. In contrast to gemfibrozil, combination of bezafibrates with statin has not so far has been found to increase the incidence of rhabdomyolysis.
**Dietary Supplements (Nutraceuticals):**

The armamentarium for lipid-lowering intervention now includes products available directly to the public as food or dietary supplements. Many patients will ask their physician about these so called “NEUTRACEUTICALS” learned of in the lay press, by word of mouth, or advertising. Such products currently marketed in the United States. Formulated as margarine-like spreads, in salad dressing, and in snack bars. These products are containing plant sterols (phytosterols) that interfere with intestinal absorption of cholesterol. The typical adult daily diet include about 0.1 percent phytosterols. Consumption 2 to 3 gm/d of plant sterols can lower LDL-C 10 to 15% with few untoward effects. Combination of these products with statins may help some patients achieve an LDL-C goal. However the formulations are high calorie and would be best substitute for butter or margarine already includes in the patient’s diet. The suggested intake of three servings a day, especially if used on bread, might increase body weight also, phytosterol-enriched foods containing trans fatty acids or saturated fat (sometime included in the salad dressing and snack bars) might have a less salubrious effect on lipid profile.

Other dietary products patients may take or ask about include psyllium, folate(commonly found enriched in food) natural phytoestrogens, soy, green tea, and synthetic fat substitutes(Olean). Cholestin, a controversial over-the-counter dietary supplement, contains a biologically active statin derived from red yeast found on rice. When devising treatment plans and counseling patients, the physician should bear in mind that scant clinical trial evidence currently cardiovascular event reduction with neutraceuticals.

**Patient with Diabetes and insulin resistance:**

Three fourth of all deaths among diabetic patients result from coronary heart disease. Compared to unaffected individuals, diabetic patient have a greater atherosclerotic burden both in major arteries and in the microvascular circulation. Not surprising, diabetic patients have substantially increased rate of atherosclerotic complications both in setting of primary prevention and after coronary interventional procedures. Thus, insulin resistance and diabetes rank among the major cardiovascular risk factors. Patients with diabetes have threefold increased rates of future cardiovascular events, with even higher rates reported among diabetic women. The risk of coronary disease among premenopausal diabetic women resembles that of nondiabetic men, indicating that diabetes largely mitigates the protective effect of female gender. Hyperglycemia is associated closely with microvascular disease, insulin resistance itself promotes atherosclerosis even before it produces frank diabetes. Recent studies corroborate the role of insulin resistance as an independent risk factor for atherothrombosis. This finding has prompted recommendations for increased surveillance for insulin resistance syndrome, a cluster of glucose intolerance and hyperinsulinemia accompanied by hypertriglyceridemia, low HDL level, and a predominance of small dense LDL particles. Insulin resistance also produces a prothromboitic state due to increased level of PAI-1 and...
fibrinogen.\textsuperscript{42,43} In addition to these systemic metabolic abnormalities, hyperglycemia causes accumulation of advanced glycation end product inculpated in vascular damage.\textsuperscript{44} Diabetic patient have markedly impaired endothelial and smooth muscle function\textsuperscript{45,46} and appear to have increased leukocyte adhesion to vascular endothelium, a critical early step atherogenesis. Diabetic nephropathy, detected by microalbuminuria predicts both cardiovascular and all cause mortality.\textsuperscript{47,48}

Pathologically features of dyslipidemia in type 2 diabetes patients are: the presence of an excessive amount of small dense LDL particles with a not excessively increased concentration of LDL-c, increased plasma triglycerides and reduced HDL-c. The combination of these components is known as the atherogenic lipid triad. Treatment must be aimed at lowering LDL-c as the main therapeutic objective\textsuperscript{49} without ignoring strategies aimed at reducing triglycerides and increasing HDL-c when altered. In order to control atherogenic dyslipidemia optimal control of diabetes must be optimized together with appropriate control of blood pressure, the promotion of healthy dietary habits like the Mediterranean diet, regular physical exercise and stop smoking.\textsuperscript{50,51} A comprehensive approach and intensive intervention on all risk factors should be implemented in everyday clinical practice to reduce the high cardiovascular morbidity and mortality that diabetic patients present, as revealed by the STENO study.\textsuperscript{52}

**Patient with hypertension:**

In contrast to cigarette consumption, hypertension is often a silent cardiovascular risk factor. Of the estimated more than 50 million Americans with high blood pressure, almost a third evades diagnosis and only a fourth receives effective treatment.\textsuperscript{53} Elevated blood pressure consistently correlate with elevated risk of stroke and myocardial infarction. Even among individuals without diastolic hypertension, isolated increases in systolic pressure are risk factor. Isolated systolic hypertension markedly increases risk for nonfatal myocardial infarction and cardiovascular death among both general population samples.\textsuperscript{54} and apparently low risk groups.\textsuperscript{55} Pulse pressure, a potentially surrogate for vascular wall stiffness, also potential predicts both first and recurrent myocardial infraction.\textsuperscript{56} Interestingly, both isolated systolic hypertension and pulse pressure independently predict coronary risk. Pharmacological reductions in diastolic blood pressure of 5 to 6 mmhg appear to reduce the risk of stroke by over 40 percent, the risk of vascular mortality by 21 percent, and the risk of coronary heart disease by 14 percent.\textsuperscript{57} In the elderly and randomized trial data have also indicated the efficacy of treating isolated systolic hypertension,\textsuperscript{58,59} all most of compliant patients, sodium reduction and weight loss can be effective.\textsuperscript{60} Joint national committee and prevention, detection, evaluation and treatment of high blood pressure continue to stress weight loss, alcohol reduction, increased physical activity, and sodium restriction as first line approaches, the proportion of hypertensive patients being treated pharmacologically will continue to increase. As with smoking cessation, programs of blood pressure control have consistently been found cost effectively.\textsuperscript{61}
CONCLUSION

Dyslipidemia is major risk of cardiovascular disease in the country even world. Smoking cigarette, obesity, unhealthy diet, sedentary lifestyle (no physical activity), alcohol are main cause of morbidity and mortality in the developing country as well as developed country. Cessation cigarette (smoking) consumption constitutes the single most important intervention in preventive cardiology. Smoking cessation alone reduces the risk of first heart attack. Modification of lifestyle, weight control by daily running or increase physically activity. Significant reduction of cardiovascular event in the high risk patient by medication such as statins, fibric acid derivatives, resins, dietary supplementary, niacin etc.

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