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Hyperlipidemia: Etiology and Possible Control

Onwe PE* ., Folawiyo MA., Anyigor -Ogah CS., Umahi G., Okorocha AE and Afoke AO
**Department of Medical Physiology, Faculty of Medicine, Ebonyi State University, Abakaliki, Nigeria.*

***Abstract*:** *Hyperlipidemia is a condition characterized by an elevation of any or all lipid profile and/or lipoproteins in the blood. Although elevated low density lipoprotein cholesterol (LDL) is thought to be the best indicator of atherosclerosis risk, (Amit et al., 2011) dyslipidemia (abnormal amount of lipids in the blood) can also describe elevated total cholesterol (TC) or triglycerides (TG), or low levels of high density lipoprotein cholesterol (HDL).Hyperlipidemia is the major precursor of lipid related ailment such as atherosclerosis, coronary artery disease and also involved in sudden death syndrome. The main cause of hyperlipidemia includes changes in lifestyle habits in which risk factor is mainly poor diet i.e. with a fat intake greater than 40 percent of total calories, saturated fat intake greater than 10 percent of total calories; and cholesterol intake greater than 300 milligrams per day or treatable medical conditions (Durrington, 1995). The pathophysiology of hyperlipidemia can be studied under the two basic classification of hyperlipidemia - primary and secondary hyperlipidemia. The pathophysiology of primary hyperlipidemia involve the idiopathic hyperchylomicronemia in which defect in lipid metabolism leads to hypertriglyceridemia and hyperchylomicronemia caused by a defect in lipoprotein lipase activity or the absence of the surface apoprotein CII31. In secondary hyperlipidemia, the postprandial absorption of chylomicrons from the gastrointestinal tract occurs 30-60 min after ingestion of a meal containing fat that may increase serum triglycerides for 3-10 hours (Bennett, 2005). Here we x-rayed the root causes of various hyperlipidemia, their clinical manifestation and possible treatment ranging from pharmacological to change in dieting. Improved lifestyle or healthy lifestyle may be a possible way out from lipid related diseases.*

Keywords: *Lipoproteins, hyperlipidemia, hypercholesterolemia, atherosclerosis and statin.*

I. Introduction

Hyperlipidemia is a medical condition characterized by an elevation of any or all lipid profile and/or lipoproteins in the blood. It is also called hypercholesterolemia/hyperlipoproteinemia (Amit et al., 2011). Although elevated low density lipoprotein cholesterol (LDL) is thought to be the best indicator of atherosclerosis risk, (Amit et al., 2011) dyslipidemia (abnormal amount of lipids in the blood) can also describe elevated total cholesterol (TC) or triglycerides (TG), or low levels of high density lipoprotein cholesterol (HDL). Human body is complex machine for maintaining the homeostasis of various organ and organ system. Any undesirable change will disturb the balance resulting in diseased state (Virchow and Thrombose, 1856). Lipids are fats in the blood stream, commonly divided into cholesterol and triglycerides. Cholesterol circulates in the bloodstream and is involved in the structure and function of cells. Triglycerides (TG) are best viewed as energy that is either used immediately or stored in fat cells. TG is manufactured in the liver from the foods or by being absorbed from the intestine (Ankur et al., 2012). Virchow in 19th century who identified cholesterol crystals in atherosclerotic lesion and stated that endothelial cell injury initiates atherogenesis (Virchow and Thrombose, 1856).

In a modification of this hypothesis it was proposed that the endothelium normally influences the behaviour of arterial smooth muscle cells by providing a barrier to the passage of plasma proteins,and that the major effect of haemodynamic or other factors that injure endothelium is to reduce the effectiveness of the barrier (Ross and Glomset, 1976). Arteries are normally smooth and unobstructed on the inside, but in case of increased lipid level, a sticky substance called plaque is formed inside the walls of arteries. This leads to reduced blood flow, leading to stiffening and narrowing of the arteries. It has been proved that elevated plasma levels of cholesterol and of LDL are responsible for atherosclerosis in man, and epidemiological data suggests that elevated plasma levels of HDL have a protective effect (Grundy and Vega, 1998). This medical condition or problem is divided into two subtypes: primary hyperlipidemia and secondary hyperlipidemia.

Primary hyperlipidemia

This usually take place as a result of genetic problems i.e., mutation within receptor protein, which may be due to single (monogonic) gene defect or multiple (polygenic) gene defect. This type may occur as a result of

change in dietary and lack of proper physical activities. See table below for summaries the various classes of primary hyperlipidemia.

TYPE	DISORDER	CAUSE	OCCURANCE	ELEVATED PLASMA LIPOPROTEIN
I.	Familial lipoprotein lipase deficiency	Genetic	Very rare	Chylomicrons
IIa	Familial hypercholesterolemia	Genetic	Less common	LDL
IIb	Polygenic hypercholesterolemia	Multifactorial	Commonest	LDL
III	Familial dysbetalipoproteinemia	Genetic	Rare	IDL, Chylomicrons Remnants
IV	Hypertriglyceridemia	Multifactorial Genetic	Common	VLDL
V	Familial combined hyperlipidemia	Genetic	Less common	VLDL,LDL

Secondary hyperlipidemia

This arises as a result of other underlining diseases like diabetes, myxoedema, nephritic syndrome, chronic alcoholism, with use of drugs like corticosteroids, oral contraceptives, Beta blockers (Joseph, 2005).

Causes of Hyperlipidemia

The main cause of hyperlipidemia includes changes in lifestyle habits in which risk factor is mainly poor diet i.e. with a fat intake greater than 40 percent of total calories, saturated fat intake greater than 10 percent of total calories; and cholesterol intake greater than 300 milligrams per day or treatable medical conditions (Durrington, 1995).The abnormal cholesterol levels are the result of an unhealthy lifestyle including taking high-fat diet and other lifestyle factors like being overweight, smoking heavy alcohol use and lack of exercise. Other factors include diabetes, kidney disease, pregnancy, and an underactive thyroid gland (Kelly, 2010). Other illnesses that may elevate cholesterol levels include polycystic ovarian syndrome and kidney disease.

The higher levels of female hormones like estrogen, have been noted to increase or change cholesterol levels. In addition, drugs like diuretics, beta-blockers and medicines used to treat depression have also been reported to raise cholesterol levels (Lipman et al., 2000). Another modifying factors in the development and progression of hyperlipidemia are age and gender. It has been shown that cholesterol levels rise as the person gets older (Lipman et al., 2000). Heredity has also been a modifying factor for the progression of hyperlipidemia as it has been noted that the genes partly determine the amount of cholesterol body makes (Durrington, 1995). Durrington, (1995), described other factors that cause hyperlipdemia without any prevalence information which are presented in table 2 below. It has also been noted that chronic renal failure, metabolic syndrome and nephrotic syndrome can predispose to hyperlipidemia are (Durrington, 1995).

S/N	Other Causes of Hyperlipidemia	Description and characteristics
1	**Berardinelli-Seip congenital lipodystrophy- hyperlipidemia**	A rare genetic disorder having heptomegaly, genetic disorder characterized by diabetes mellitus, loss of body fat, enlarged genitals, increased skeletal growth and other abnormalities.
2	**Berardinelli-Seip congenital lipodystrophy, type 1 - hyperlipidemia**	A rare genetic disorder caused by a defect on the AGPAT2 gene on chromosome 9q34.326 characterized by early-onset diabetes mellitus, loss of body fat, serious insulin resistance, high blood triglycerides and fatty liver (Durrington, 1995).
3	**Berardinelli-Seip congenital lipodystrophy, type 2 - hyperlipidemia**	A rare genetic disorder caused by a defect on the BSCL2 gene on chromosome 11q13 by early-onset diabetes mellitus, loss of body fat, serious insulin resistance, high blood triglycerides and fatty liver (Seip, 1959).
4	**Cholestasis**	A condition the bile flow from the liver to the duodenum is blocked. It is of two types first one is caused by mechanical blockage in the duct system which occur from a gallstone or malignancy and other type is metabolic cholestasis, in which disturbances in bile formation occur because of genetic defects or acquired as a side effect of many medications (Trauner *et al.*, 1998).
5	**Chromosome 15q, deletion**	A rare chromosomal disorder which occurs because of deletion of genetic material from the long arm of chromosome 15 (Chaer *et al.*, 2004)
6	**Neuropathy, hereditary motor and sensory, Okinawa type**	This is a dominantly inherited, slow-progressing motor and sensory nerve disease which primarily involves the
		proximal muscles (i.e. the muscles closest to the trunk of the body) (Takashima, 1997).

Pathophysiology of hyperlipidemia

The pathophysiology of hyperlipidemia can be studied under the two basic classification of hyperlipidemia. The pathophysiology of primary hyperlipidemia involve the idiopathic hyperchylomicronemia in which defect in lipid metabolism leads to hypertriglyceridemia and hyperchylomicronemia caused by a defect in lipoprotein lipase activity or the absence of the surface apoprotein CII31.Moreover, hyperchylomicronemia in cats with autosomal recessive defect in lipoprotein lipase (LPL) activity showed the occurrence of primary hyperlipidemia (Gotto and Moon, 2010).

In secondary hyperlipidemia, the postprandial absorption of chylomicrons from the gastrointestinal tract occurs 30- 60 min after ingestion of a meal containing fat that may increase serum triglycerides for 3-10 hours (Bennett, 2005).The diabetes mellitus patients have been noted to possess low LPL activity which further caused high synthesis of VLDL cholesterol by the liver ultimately leading to hyperlipidemia. Moreover, hypothyroidism-induced low LPL activity and lipolytic activity has been noted to reduce hepatic degradation

of cholesterol to bile acids. Furthermore, hyperadrenocorticism increased the synthesis of VLDL by the liver causing both hypercholesterolemia and hypertriglyceridemia (Stone, 1994 and Baron, 2005). Liver disease hypercholesterolemia has been noted to be caused by reduced excretion of cholesterol in the bile. Furthermore, in nephrotic syndrome, the common synthetic pathway for albumin and cholesterol causes low oncotic pressure ultimately leading to enhanced cholesterol synthesis (Castilla-Guerra et al., 2009).

The response-to-injury hypothesis states that risk factors such as oxidized LDL, mechanical injury to the endothelium, excessive homocysteine, immunologic attack, or infection-induced changes in endothelial and intimal function lead to endothelial dysfunction and a series of cellular interactions that culminate in atherosclerosis. The eventual clinical outcomes may include angina, myocardial infarction, arrhythmias, stroke, peripheral arterial disease, abdominal aortic aneurysm, and sudden death (Castilla-Guerra et al., 2009).

Atherosclerotic lesions are thought to arise from transport and retention of plasma LDL through the endothelial cell layer into the extracellular matrix of the subendothelial space.

Once in the artery wall, LDL is chemically modified through oxidation and nonenzymatic glycation. Mildly oxidized LDL then recruits monocytes into the artery wall. These monocytes then become transformed into macrophages that accelerate LDL oxidation (Castilla-Guerra et al., 2009).

Oxidized LDL provokes an inflammatory response mediated by a number of chemoattractants and cytokines (e.g., monocyte colony-stimulating factor, intercellular

adhesion molecule, platelet-derived growth factor, transforming growth factors, interleukin-1, interleukin-6) (Castilla-Guerra et al., 2009).

Repeated injury and repair within an atherosclerotic plaque eventually leads to a fibrous cap protecting the underlying core of lipids, collagen, calcium, and inflammatory cells such as T lymphocytes. Maintenance of the fibrous plaque is critical to prevent plaque rupture and subsequent coronary thrombosis (Stone, 1994 and Baron, 2005).

The extent of oxidation and the inflammatory response are under genetic control, and primary or genetic lipoprotein disorders are classified into six categories for the phenotypic description of hyperlipidemia. The types and corresponding lipoprotein elevations include the following: I (chylomicrons), IIa (LDL), IIb (LDL + very low density lipoprotein, or VLDL), III (intermediate-density lipoprotein, or IDL); IV (VLDL), and V (VLDL + chylomicrons). Secondary forms of hyperlipidemia also exist, and several drug classes may elevate lipid levels (e.g., progestins, thiazide diuretics, glucocorticoids, Î² blockers, isotretinoin, protease inhibitors, cyclosporine, mirtazapine, sirolimus) (Stone, 1994 and Baron, 2005).

The primary defect in familial hypercholesterolemia is the inability to bind LDL to the LDL receptor (LDL-R) or, rarely, a defect of internalizing the LDL-R complex into the cell after normal binding. This leads to lack of LDL degradation by cells and unregulated biosynthesis of cholesterol, with total cholesterol and LDL-C being inversely proportional to the deficit in LDL receptors (Barbara et al., 2005).

Clinical manifestations

The clinical manifestations of hyperlipidemia are as follows;

1. Familial hypercholesterolemia is characterized by a selective elevation in plasma LDL and deposition of LDL- derived cholesterol in tendons (xanthomas) and arteries (atheromas) (Barbara et al., 2005).
2. Familial lipoprotein lipase deficiency is characterized by a massive accumulation of chylomicrons and a corresponding increase in plasma triglycerides or a type I lipoprotein pattern. Presenting manifestations include repeated attacks of pancreatitis and abdominal pain, eruptive cutaneous xanthomatosis, and hepatosplenomegaly beginning in childhood. Symptom s everity is proportional to dietary fat intake, and consequently to the elevation of chylomicrons. Accelerated atherosclerosis is not associated with this disease (Barbara et al., 2005).
3. Patients with familial type III hyperlipoproteinemia develop the following clinical features after age 20: xanthoma striata palmaris (yellow discolorations of the palmar and digital creases); tuberous or tuberoeruptive xanthomas (bulbous cutaneous xanthomas); and severe atherosclerosis involving the coronary arteries, internal carotids, and abdominal aorta (Barbara et al., 2005).
4. Type IV hyperlipoproteinemia is common and occurs in adulthood primarily in patients who are obese, diabetic, and hyperuricemic and do not have xanthomas. It may be secondary to alcohol ingestion and can be aggravated by stress, progestins, oral contraceptives, thiazides, or Î² blockers (Barbara et al., 2005).
5. Type V is characterized by abdominal pain, pancreatitis, eruptive xanthomas, and peripheral polyneuropathy. These patients are commonly obese, hyperuricemic, and

diabetic; alcohol intake, exogenous estrogens, and renal insufficiency tend to be exacerbating factors. The risk of atherosclerosis is increased with this disorder (Barbara et al., 2005).

Diagnosis of hyperlipidemia

The following are the ways in which proper diagnosis of hyperlipidemia can be made;

1. The National Cholesterol Education Program recommends that a fasting lipoprotein profile (FLP) including total cholesterol, LDL, HDL, and triglycerides should be measured in all adults 20 years of age or older at least once every 5 years (Barbara et al., 2005).
2. Measurement of plasma cholesterol (which is about 3% lower than serum determinations), triglyceride, and HDL levels after a 12-hour or longer fast is important, because triglycerides may be elevated in nonfasted individuals; totalcholesterol is only modestly affected by fasting (Barbara et al., 2005).
3. Two determinations, 1 to 8 weeks apart, with the patient on a stable diet and weight, and in the absence of acute illness, are recommended to minimize variability and to obtain a reliable baseline. If the total cholesterol is greater than 200 mg/dL, a second determination is recommended, and if the values are more than 30 mg/dL apart, the average of three values should be used (Barbara et al., 2005). After a lipid abnormality is confirmed, major components of the evaluation are the history (including age, gender, and, if female, menstrual and estrogen replacement status), physical examination, and laboratory investigations.
4. A complete history and physical examination should assess (1) presence or absence of cardiovascular risk factors or definite cardiovascular disease in the individual; (2) family history of premature cardiovascular disease or lipid disorders; (3) presence or absence of secondary causes of hyperlipidemia, including concurrent medications; and (4) presence or absence of xanthomas, abdominal pain, or history of pancreatitis, renal or liver disease, peripheral vascular disease, abdominal aortic aneurysm, or cerebral vascular disease (carotid bruits, stroke, or transient ischemic attack) (Barbara et al., 2005).
5. Diabetes mellitus is now regarded as a CHD risk equivalent. That is, the presence of diabetes in patients without known CHD is associated with the same level of risk as patients without diabetes but having confirmed CHD (Barbara et al., 2005).
6. If the physical examination and history are insufficient to diagnose a familial disorder, then agarose-gel lipoprotein electrophoresis is useful to determine which class of lipoproteins is affected. If the triglyceride levels are below 400 mg/dL and neither type III hyperlipidemia nor chylomicrons are detected by electrophoresis, then one can calculate VLDL and LDL concentrations: VLDL = triglyceride/5; LDL = total
7. **cholesterol** - (VLDL + HDL). Initial testing uses total cholesterol for case finding, but subsequent management decisions should be based on LDL (Barbara et al., 2005).
8. Because total cholesterol is composed of cholesterol derived from LDL, VLDL, and HDL, determination of HDL is useful when total plasma cholesterol is elevated. HDL may be elevated by moderate alcohol ingestion (fewer than two drinks per day), physical exercise, smoking cessation, weight loss, oral contraceptives, phenytoin, and terbutaline. HDL may be lowered by smoking, obesity, a sedentary lifestyle, and drugs such as Î² blockers (Barbara et al., 2005).
9. Diagnosis of lipoprotein lipase deficiency is based on low or absent enzyme activity with normal human plasma or apolipoprotein C-II, a cofactor of the enzyme (Barbara et al., 2005).

To have a low risk of heart disease, the lipid levels must be maintained as follows;

1. LDL less than 130 mg/dL or < 70 if you have established diagnosis of diabetes
2. HDL greater than 40 mg/dL (men) or 50 mg/dL (women)
3. Total cholesterol less than 200 mg/dL and
4. Triglycerides less than 200 mg/dL or 150 if you have established heart disease or diabetes (Barbara et al., 2005).

Possible Treatment

The National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) recommends that a fasting lipoprotein profile and risk factor assessment be used in the initial classification of adults. There are three categories of risk that modify the goals and modalities of LDL-lowering therapy. The highest risk category is having known CHD or CHD risk equivalents; the risk for major coronary events is equal to or greater than that for established CHD (i.e., more than 20% per 10 years, or 2% per year). The intermediate category includes two or more risk factors, in which the 10-year risk for CHD is 20% or less. The lowest risk category is persons with zero to one risk factor, which is usually associated with a 10-year risk of

CHD of less than 10% (Barbara et al., 2005).
Over the past few years guidelines for the use of lipid-lowering therapy have become more aggressive following the results of major trials showing mortality benefit for the use of statins. Most guidelines recommend statin treatment for a patient with CAD with a 10-year risk that is greater than 20% (high risk) once a trial of dietary therapy has been unsuccessful. However, treatment can be cost effective with a 10-year risk of 10% (Barbara et al., 2005).

The goals of therapy are the reduction of LDL cholesterol levels and the level of initiation of therapeutic lifestyle change (TLC) and proper drug therapy are for adults and children. While these goals are surrogate end points, the primary reason to institute TLC and drug therapy is to reduce the risk first or recurrent events such as MI, angina, heart failure, ischemic stroke, or other forms of peripheral arterial disease such as carotid stenosis or abdominal aortic aneurysm (Amit et al., 2011).
Basically Treatment therapy involves two approaches, which are Non-pharmacological therapy and Pharmacological therapy

Non pharmacological therapy
The objectives of dietary therapy are to decrease the intake of total fat, saturated fatty acids (i.e., saturated fat), and cholesterol progressively and to achieve a desirable body weight ((Amit et al., 2011). This involves;

1. Reduced saturated fat intake to 7 percent of daily calories
2. Reduced total fat intake to 25 to 35 percent of daily calories
3. Limited dietary cholesterol to less than 200 mg per day
4. Eating 20 to 30 g a day of soluble fiber, which is found in oats, peas, beans, and certain fruits; and
5. Increased intake of plant stanols or sterols, substances found in nuts, vegetable oils, corn and rice, to 2 to 3 g daily. Other foods that can help control cholesterol include cold-water fish, such as mackerel, sardines, and salmon. These fish contain omega-3 fatty acids that may lower triglycerides. Soybeans found in tofu and soy nuts and many meat substitutes contain a powerful antioxidant that can lower LDL (Amit et al., 2011).

Pharmacological therapy
This involves mainly the use of drugs. The major drug involves in the treatment of hyperlipidemia is known as statin. Generally, the drugs involves in the treatment of hyperlipidemia are classified as follows;

- HMG-CoA reductase inhibitors (Statins): Lovastatin, Simvastatin, Pravastatin, Atorvastin, Rosuvastin (Belichard et al., 1993).
- Bile acid sequestrants (Resins): Cholestyramine, Colestipol.
- Activate lipoprotein lipase (Fibric acid derivatives): Clofibrate, Gemfibrozil,Benzafibrate and Fenofibrate.
- Inhibit lipolysis and triglyceride synthesis: Nicotinic acid.
- Others: Ezetimibe, Gugulipid.

Statin
This is the major drug for the treatment of hyperlipidemia also known as HMG-CoA Reductase Inhibitors (Examples are, Atorvastatin, Fluvastatin, Lovastatin, Pravastatin, Rosuvastatin, Simvastatin) mediates its functions as follows;

1. Statins inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, interrupting the conversion of HMG-CoA to mevalonate, the rate-limiting step in de novo cholesterol biosynthesis. Reduced synthesis of LDL and enhanced catabolism of LDL mediated through LDL receptors appear to be the principal mechanisms for lipid- lowering effects (Belichard et al., 1993).
2. When used as monotherapy, statins are the most potent total and LDL cholesterol- lowering agents and among the best tolerated. Total and LDL cholesterol are reduced in a dose-related fashion by 30% or more when added to dietary therapy.
3. Combination therapy with a statin and BAR is rational as numbers of LDL receptors are increased, leading to greater degradation of LDL cholesterol; intracellular synthesis of cholesterol is inhibited; and enterohepatic recycling of bile acids is interrupted.
4. Combination therapy with a statin and ezetimibe is also rational because ezetimibe inhibits cholesterol absorption across the gut border and adds 12% to 20% further reduction when combined with statin or other drugs.

Constipation occurs in fewer than 10% of patients taking statins. Other adverse effects include elevated serum aminotransferase levels (primarily alanine aminotransferase), elevated creatine kinase levels, myopathy, and rarely rhabdomyolysis (Diebold et al., 1994).

Bile acid resins (cholestyramine, colestipol, colesevelam)

1. The primary action of bile acid resins (BARs) is to bind bile acids in the intestinal lumen, with a concurrent interruption of enterohepatic circulation of bile acids, which decreases the bile acid pool size and stimulates hepatic synthesis of bile acids from cholesterol. Depletion of the hepatic pool of cholesterol results in an increase in cholesterol biosynthesis and an increase in the number of LDL receptors on the hepatocyte membrane, which stimulates an enhanced rate of catabolism from plasma and lowers LDL levels. The increase in hepatic cholesterol biosynthesis may be paralleled by increased hepatic VLDL production and, consequently, BARs may aggravate hypertriglyceridemia in patients with combined hyperlipidemia (Diebold et al., 1994).
2. BARs are useful in treating primary hypercholesterolemia (familial hyper-cholesterolemia, amilial combined hyperlipidemia, type IIa hyperlipoproteinemia).
3. Gastrointestinal complaints of constipation, bloating, epigastric fullness, nausea, and flatulence are most commonly reported. These adverse effects can be managed by increasing fluid intake, modifying the diet to increase bulk, and using stool softeners.
4. The gritty texture and bulk may be minimized by mixing the powder with orange drink or juice. Colestipol may have better palatability than cholestyramine because it is odourless and tasteless. Tablet forms should help improve adherence with this form of therapy.

Other potential adverse effects include impaired absorption of fat-soluble vitamins A, D, E, and K; hypernatremia and hyperchloremia; gastrointestinal obstruction; and reduced bioavailability of acidic drugs such as warfarin, nicotinic acid, thyroxine, acetaminophen, hydrocortisone, hydrochlorothiazide, loperamide, and possibly iron. Drug interactions may be avoided by alternating administration times with an interval of 6 hours or greater between the BAR and other drugs (Diebold et al., 1994).

Fibric acids (gemfibrozil, fenofibrate, clofibrate)

1. Fibrate monotherapy is effective in reducing VLDL, but a reciprocal rise in LDL may occur and total cholesterol values may remain relatively unchanged. Plasma HDL concentrations may rise 10% to 15% or more with fibrates.
2. Gemfibrozil reduces the synthesis of VLDL and, to a lesser extent, apolipoprotein B with a concurrent increase in the rate of removal of triglyceride-rich lipoproteins from plasma. Clofibrate is less effective than gemfibrozil or niacin in reducing VLDL production.
3. Gastrointestinal complaints occur in 3% to 5% of patients, rash in 2%, dizziness in 2.4%, and transient elevations in transaminase levels and alkaline phosphatase in 4.5% and 1.3%, respectively. Clofibrate and, less commonly, gemfibrozil may enhance the formation of gallstones.
4. A myositis syndrome of myalgia, weakness, stiffness, malaise, and elevations in creatine kinase and aspartate aminotransferase may occur and seems to be more common in patients with renal insufficiency.
5. Fibrates may potentiate the effects of oral anticoagulants, and the international normalized ratio (INR) should be monitored very closely with this combination.

Niacin

1. Niacin (nicotinic acid) reduces the hepatic synthesis of VLDL, which in turn leads toa reduction in the synthesis of LDL. Niacin also increases HDL by reducing its catabolism.
2. The principal use of niacin is for mixed hyperlipidemia or as a second-line agent in combination therapy for hypercholesterolemia. It is a first-line agent or alternative for the treatment of hypertriglyceridemia and diabetic dyslipidemia.
3. Niacin has many common adverse drug reactions; most of the symptoms and biochemical abnormalities seen do not require discontinuation of therapy.
4. Cutaneous flushing and itching appear to be prostaglandin mediated and can be reduced by taking aspirin 325 mg shortly before niacin ingestion. Taking the niacin dose with meals and slowly titrating the dose upward may minimize these effects. Concomitant alcohol and hot drinks may magnify the flushing and pruritus from niacin, and they should be avoided at the time of ingestion. Gastrointestinal intolerance is also a common problem.
5. Potentially important laboratory abnormalities occurring with niacin therapy include elevated liver function tests, hyperuricemia, and hyperglycemia. Niacin-associated hepatitis is more common with sustained-release preparations, and their use should be restricted to patients intolerant of regular-release

products. Niacin is contraindicated in patients with active liver disease, and it may exacerbate preexisting gout and diabetes (Belichard et al., 1993). Nicotinamide should not be used in the treatment of hyperlipidemia because it does not effectively lower cholesterol or triglyceride levels.

Ezetimibe

Ezetimibe interferes with the absorption of cholesterol from the brush border of the intestine, a novel mechanism that makes it a good choice for adjunctive therapy. It is approved as both monotherapy and for use with a statin. The dose is 10 mg once daily, given with or without food. When used alone, it results in an approximate 18% reduction in LDL cholesterol. When added to a statin, ezetimibe lowers LDL by about an additional 12% to 20%. A combination

product (Vytorin) containing ezetimibe 10 mg and simvastatin 10, 20, 40 or 80 mg is available. Ezetimibe is well tolerated; approximately 4% of patients experience gastrointestinal upset. Because cardiovascular outcomes with ezetimibe have not been evaluated, it should be reserved for patients unable to tolerate statin therapy or those who do not achieve satisfactory lipid lowering with a statin alone (Belichard et al., 1993).

Fish oil supplementation

1. Diets high in omega-3 polyunsaturated fatty acids (from fish oil), most commonly eicosapentaenoic acid (EPA), reduce cholesterol, triglycerides, LDL, and VLDL and may elevate HDL cholesterol.
2. Fish oil supplementation may be most useful in patients with hypertriglyceridemia, but its role in treatment is not well defined.
3. Complications of fish oil supplementation such as thrombocytopenia and bleeding disorders have been noted, especially with high doses (EPA, 15 to 30 g/day) (Barbara et al., 2005)

II. Conclusion

Hyperlipidemia refers to elevated levels of lipids and cholesterol in the blood and is also identified as dyslipidemia. Although elevated low density lipoprotein cholesterol (LDL-C) is thought to be the best indicator of atherosclerosis risk. Dyslipidemia can also be view as elevated total cholesterol (TC) or triglycerides (TG), or low levels of high density lipoprotein cholesterol (HDL-C). Hyperlipidemia can be control pharmacologically and most importantly via change in lifestyle especially dieting.

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