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An update on hyperlipidemia and its management

R A. Memon
Aga Khan University

A H. Gilani
Aga Khan University, anwar.gilani@aku.edu

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Riaz A. Memon, Anwar H. Gilani (Department of Physiology and Pharmacology, Faculty of Health Sciences, The Aga Khan University, Karachi.)

Introduction

Excessive accumulation of one or more of the major lipids in plasma can produce a marked increase in the risk of coronaiy heart diseases and other vascular complications. Increased levels of serum total cholesterol and more specifically low density lipoprotein are a major risk factor for cardiovascular diseases. There is substantial evidence that appropriate treatment can reduce this risk[1,2]. Decreased high density lipoprotein levels are also an important risk faqtor[1,2], whereas, the role of increased serum triglyceride levels as an independent risk factor is still being debated[3]. The accumulation of one or more lipoprotein fractions can either be due to defective removal from ‘plasma or increased endogenous production or both. These mechanistic abnormalities may beprimaiy ormay result secondary to other diseases such as diabetes mellitus, nephrotic syndrome, uremia, hypothyroidism, chronic infections, and malignancies[4-7]. Several commonly used drugs suchasgiucocorticoids, oral contraceptive pills, thiazide diuretics, beta-blockers and interferons can also produce significant increase in serum lipoprotein levels[7,8]. In this review we will briefly describe the physiology and biochemistry of various lipoproteins and the different causes of hyperlipidernia. We will also provide an update on the basic principles in the management of hyperlipidemia and the guidelines for the rational drug therapy in various disorders of lipid and lipoprotein metabolism.

Biochemistry and Physiology of Lipoproteins

Lipoproteins are macromolecular complexes carrying various lipids and proteins in the plasma. The major lipids of lipoproteins are free and estenfied cholesterol, TGs and phospholipids. Triglycerides (TO) and cholesterol esters are hydrophobic and constitute the core of lipoproteins. Phospholipids and free cholesterol, which are soluble in both lipid and aqueous environments, cover the surface of the lipoproteinparticleswhere they actas aninterfacebetweenthe plasma and core components. In addition to phospholipids and free cholesterol, there is a group of proteins which also occupy the surface of lipoproteins and are called apolipoproteins or apoproteins. These apoproteins play an important role in the regulation of lipid transport and lipoprotein metabolism[9]. The lipoproteins have been subdivided into five major classes on the basis of their physical and chemical characteristics as they vary in density, size, source of origin, lipid composition and function. These classes include chyloniicrons, very low density lipoproteins (VLDL), intermediate density lipoproteins (IDL), low density lipoproteins (LDL) and high density lipoproleins (HDL). The major characteristics of these lipoprotein classes are summarized in Table I.

Table I. Classes of plasma lipoproteins and their characteristics.

Lipoprotein	Density (g/dl)	Diameter (nm)	Origin	Lipid composition (%)	Major Functions
Chylomicrons	<0.95	75-1200	Intestine	TG:80-90 Chol:2-7 PL:3-9	Transport of dietary TGs
Very low density lipoproteins	<0.95-1.006	30-80	Liver	TG:55-80 Chol:5-15 PL:10-20	Transport of endogenously synthesized TGs
Intermediate density lipoproteins	1.006-1.019	25-35	Metabolism of VLDL	TG:20- 50 Chol:20-40 PL:15-25	Transport of endogenous Cholesterol
Low density lipoproteins	1.019-1.063	18-25	Metabolism of VLDL and IDL	TG:5-15 Chol:40-50 PL:10-14	Transport of cholesterol esters of hepatic and intravascular origin
High density lipoproteins	1.063-1.21	5-12	Liver, intestine, intravascular metabolic reactions	TG: 5-10 Chol:15-25 PL:20-30	Facilitates removal of Cholesterol from extra-hepatic tissues

*Apolipoproteins make up the rest.
Abbreviations: TGs; triglycerides, Chol: cholesterol, PL; phospholipids.

Triglycerides are the major lipids in chylomiçrons and VLDL. They serve as energy substrates in the liver and peripheral tissues. Energy is also stored in the form of TGs in the adipose tissue. Most TG molecules in chylornicron and VLDL are hydrolyzed by lipoproteinlipase (LPL) and hepatic TGlipase (HTGL). The fatty acids released by these reactions are taken up by the liver, muscle and adipose tissue. TGs can also be transferred between TG-nch and cholesterol-rich lipoproteins in association with a carrier protein known as cholesterol ester transfer protein[10]. Cholesterol is present in all the lipoproteins but it is the major component of LDL, IDL and HDL. Cholesterol is not used for energy but it serves as a structural component of all cell membranes. It is also a precursor for adrenal and gonadal steroids and hepatic bile acids. Inlipoproteinparticles, most of the cholesterol is found in the form of cholesterol esters in the core. The majorcholesterol ester is cholesterol linoleate which is formed in the plasma by the action of lecithin cholesterol acyltransferase (LCAT) enzyme. A small proportion of lipoprotein cholesterol is carried as free cholesterol in the surface of lipoprotein particles. Phospholipids, which are the component of all cell membranes, make up the majority of surface of lipoproteins. They form a lipid layer that acts as an interface with both the polar plasma environment and the non-polar lipids of the lipoprotein core. Phosphotidyicholine (lecithin) is the major phospholipid in plasma and is the source of linoleate for cholesterol ester formation by LCAT reaction. Different apoproteins are found on the surface of lipoproteins. In addition to providing structural stability to lipoproteins, they also have a critical role in the regulation of lipoprotem metabolism[9]. Some of them are essential for the synthesis and secretion of chylomicrons and VLDL whereas others act as ligand for the binding of lipoproteins to their receptors. Some of the apoproteins act as co-factor for plasma enzymes such as LPL and LCAT. The deficiency or abnormal function of these apoproteins can result in abnormalities in lipid meabolism[11,12].The well characterized apoproteins and their major metabolic functions are listed in Table II.

Causes of Hyperlipidemia

The intravascular concentrations of various lipoprotein particles orthe concentrations of plasma lipidsare determined by the balance between the rate of formation of lipoproteins and the rates of their degradation and/or cellular uptake. Disruption of this balance can lead to hyperlipidemia which may manifest as hypercholesterolernia or hypertriglyceridemia or a combination of both. The abnormalities of lipoprotein metabolism may be primary in origin or may occur secondary to other diseases or

therapy with certain drugs or hormones[13,14]. The primary types of hyperlipidemia are generally divided into familial and sporadic forms. In familial type there is a clear evidence of genetic predisposition based on the presence of the disorder in closely related family members whereas in the sporadic variety no known genetic factor or secondary cause is present. The primary and secondary hyperlipidernia are generally characterized by similar laboratory abnormalities, however, the magnitude of the changes in plasma lipid levels may be variable. It is important to differentiate between primary and secondary hyperlipidemia from a therapeutic point of view, as the secondary hyperlipidemia may be corrected by treatment of causative disease or by withdrawal of the drug responsible for producing the abnormality. Classically, hyperlipidemia have been classified into six types on the basis of specific electrophoretic patterns of various lipoproteins in plasma[15]. According to this classification the patients with different disorders of lipid metabolism may have an excess of chylomicrons (type I), elevated LDL (type HA), or an increase in both LDL and VLDL (Type IIB) levels. In some rare familial disorders there is excessive accumulation of VLDL remnant particles (type III). Anexcess of VLDL alone (type IV) or VLDL and chylornicrons(typeV) may also occur in several pr mary and secondary disorders of TG metabolism. However, studies have shown that these plasma lipoprotein patterns are not specific to various primary and secondary disorder of lipoprotein metabolism. The plasma lipoprotein patterns may change overtime in individuals as VLDL is converted to IDL and LDL. Them are also profound effects of diet on lipoprotein metabolism[16]. Thus, classificationsbasedonthetype of plasma lipoprotein patterns may not reflect the genetic or pathophysiologic mechanisms responsible for various disorders. A single mechanism may lead to several different lipoprotein patterns while a single pattern may result from a variety of diseases or mechanisms. From a pathophysiologic perspective the disorders of lipoprotein metabolism may either be due to an increase in endogenous production of lipoproteins or a defect in their removal or a combination of both mechanisms. Increased endogenous production is usually due to an increase in hepatic VLDL synthesis and secretion and is commonly seen in familial hypertriglyceridernia, diabetes mellitus, acromegaly, cushing's syndrome, chronic alcoholism and prolonged use of corticosteroids and oral contraceptives[13,14] . On the other hand, defective removal of lipoproteins can occur at three different sites along the lipoproteintransport pathway. It could be due to a defect in the cellular uptake of LDL secondaiy to a deficiency or absence of LDL receptors, defective removal of remnant particles due to mutations in apo F gene, or decreased catabolism of TG-rich lipoprotein due to deficiency or abnormal function of lipoprotein lipase enzyme[13,14].

Table III. Classification of the hyperlipidemias based on their pathophysiology.

Mechanism	Disorders Primary	Secondary	Plasma lipoprotein pattern
Increased production			
Increase VLDL synthesis	Familial hypertriglyceridemia	Diabetes mellitus Acromegaly Obesity Glucocorticoid therapy Oral contraceptives Alcohol Thiazide diuretics	Type IV and V
Defective removal			
Decreased LDL removal	Familial hypercholesterolemia Familial defective apo B-100	Hypothyroidism	Type IIA and IIB
Abnormal LPL function	Lipoprotein lipase deficiency Apo C-II deficiency	Type I diabetes mellitus Chronic renal failure	Type I, IV and V
Decreased remnant removal	Dysbetalipoproteinemia	Beta-adrenoceptor blockers	Type III
Increased production and	Polygenic hypercholesterolemia Familial combined hyperlipidemia	Nephrotic syndrome	Type IIA, IIB, IV

Table III presents a classification of common causes of hyperlipidemia based on the pathophysiologic

mechanism involved.

Management of Hyperlipidemia

In order to treat patients with hyperlipidemia, the therapeutic approach should focus on reducing the overall cardiovascular risk. After taking a family and personal history of cardiovascular disease, an effort should be made to identify secondary causes of hyperlipidernia such as inappropriate diet, uncontrolled diabetes mellitus, undiagnosed or untreated hypothyroidism and drug which may alter lipid metabolism. Smoking status, exettise level and degree of obesity should also be determined. In many patients a serious and sincere effort which reduces these risk factors through changes in life style and therapy of specific diseases can produce a substantial decrease in serum lipid levels, reduce the risk of cardiovascular diseases and may nepte the need for specific anti-hyperlipidemic drug therapy[17]. The first step in the management of hyperlipidemia is usually the nutritional counselling and dietary therapy[18]. The patients should be advised to reduce their fat intake to less than 30% of their total caloric intake and saturated fatty acid should be less than 10% of total caloric intake; the rest of the fat calories should come from poly-unsaturated and mono-unsaturated fatty acids in a roughly equal ratio. At this stage, the dietary intake of cholesterol should be less than 300 mg/day. If the serum lipid levels do not respond to these changes within three months, then a further reduction in total fat intake is usually necessary. In this dietary regimen saturated fatty acid should constitute less than 7% of total caloric intake and total cholesterol intake should be less than 200 mg/day. The patients who do not respond to changes in life style and diet should be treated with specific anti-hyperlipidemic drugs depending upon their lipid profile. Patients with a history of ischemic heart disease should be aggressively treated by minimizing other cardiovascular risk factors and maximizing the control of serum lipoprotein levels. In most cases this approach has been shown to reduce the progression of atherogenesis and subsequent morbidity and mortality associated with cardiovascular diseases[19,20]. Recently specific guidelines have been developed by the Adult Treatment Panel of the National Cholesterol EducationProgmmme(NCEP)ofUnited States which utilizes LDL levels for assessing the risk of heart disease and for treatment recommendations[21]. Similarly specific guidelines for the management of hypertriglyceridemia have also been developed[22]. Both of these panels have classified total cholesterol, LDL-cholesterol and TO levels as desirable, borderline and high risk (Table IV).

Table IV. Classification of total cholesterol, LDL cholesterol and triglyceride levels*.

Classification	Total Cholesterol (mg/dl)	LDL-Cholesterol (mg/dl)	Triglycerides (mg/dl)
Desirable	<200	<130	<250
Borderline	200-239	130-159	250-500
High-risk	>240	>160	500

*The classification is based on the data from the National Cholesterol Education panel, USA (JAMA 269:3015-3023, 1993) and NIH Consensus Conference on Hypertriglyceridemia (JAMA 269:505- 510, 1993).

A low HDL-cholesterol (<30 mg/dl) is also considered as a major risk factor whereas high HDL-cholesterol (>60 mg/dl is considered protective against coronary heart disease[21]. It has been suggested that hyperlipidemic patient should receive specific medical therapy according to their degree of risk

and serum lipoprotein levels[21,22]. A high degree of risk has been defined as a personal history of cardiovascular diseases or two or more major risk factors which include male sex, hypertension, smoking, diabetes mellitus, obesity, family history of heart disease and low levels of HDL-cholesterol[21,22]. The goal of the drug therapy is to bring the serum lipoprotein levels in the desirable range. However, one should not be over-enthusiastic in lowering plasma lipid levels beyond the desirable range as hypolipidemia can also have some undesirable effects such as increased predisposition to certain types of cancer and increased susceptibility to the harmful effects of endotoxin[7]. Drug therapy for hyperlipidernia should be supplernentary to dietary therapy and changes in life style without which it is unlikely to succeed. At present a w'ide variety of lipid lowering agents with distinct mechanisms of action and pharmacological effects are available. These drugs include HMG-CoA reductase inhibitors, bile acid binding resins, fibric acid derivatives, nicotinic acid, probucol and several traditional remedies. Several extensive reviews on the pharmacology of anti-hyperlipidemic drugs have been published2325. As discussed under the causes of hyperlipidemia, plasma lipoprotein pattern are not very specific to various primary and secondary disorders. More than one lipoprotein pattern may occur in a particular disease or condition and similarly several diseases may produce a common biochemical abnormality in lipid metabolism. From a therapeutic viewpoint patients with hyperlipidemia usually have one of the following four distinct plasma lipoprotein profiles (Table V).

Table V. Common blood lipid profiles and the drugs of choice for management.

Lipid profile	Drug of choice*
High LDL and normal triglycerides	HMG-CoA reductase inhibitors Bile acid binding resins Combined drug therapy
High Triglycerides and normal LDL	Fibric acid derivatives Nicotinic acid
High LDL and high triglycerides	Nicotinic acid Fibric acid derivatives+HMG-CoA reductase inhibitors
Low HDL with normal or high triglycerides and LDL	Fibric acid derivatives Nicotinic acid HMG-CoA reductase inhibitors

*Drug groups are listed in order of first to last choice based on their effects on various lipoprotein classes. However, these are only guidelines and the final selection of drug should take into account secondary causes, other cardiovascular risk factors, patient's life style, anticipated side effects and the desired benefits for the individual patient.

Each of these patterns may represent a different disease process and may require a unique therapeutic approach (Table V).

Common lipid profiles and their management

A) High LDL and normal TG levels

Patients with a high LDL levels usually have an elevated total cholesterol levels and a normal or nearly normal plasma TG levels. The major primary causes of this lipoprotein pattern include polygenic hypercholesterolemia, familial combined hyperlipidernia and familial hypercholesterolemia[13]. While theexact moleculardefectinthefirst two disorders have not been characterized, familial hyper-cholesterolemiais due to decreased expressionof hepatic LDL receptors[26]. Heterozygous type of this disorder is quite common with an incidence rate of 1 in 500 in general populationwhile the homozygous type is very rare. A decrease in the expression of hepatic LDL receptors leads to reduced catabolism of LDL resulting in increased plasma levels. The decreased LDL turnover also leads to prolonged LDL exposure to the endothelium and increased formation of oxidized LDL particles. These oxidized LDL particles have a high affinity for macrophage scavenger receptors resulting in their deposition in the arterial wall and enhanced atherogenesis[27]. In patients with an elevated LDL levels, drug therapy is directed at enhancing the expression of LDL receptors which can increase receptor mediated LDL catabolism. This goal is accomplished by the use of HMG-CoA reductase inhibitors and bile acid binding resins. HMG-CoA reductase inhibitors such as lovastatin, pravastatin and simvastatin interfere with cholesterol synthesis by inhibiting HMG-CoA reduclase, the rate limiting enzyme in cholesterol biosynthesis[28]. As a result there is a decrease in the hepatic cholesterol synthesis and a subsequent reduction in the intracellular pool of cholesterol. This leads to a compensatory increase inthe expression of high affinity LDL receptors on the cell surface resulting in enhanced receptor mediated clearance of LDL and a further reduction in plasma LDL levels[28]. Studies have shown that lovastatin, pravastatin and simvastatin produce a dose-dependent decrease inLDL levels to the extent of 30-40%. They also produce a 15-20% decrease in plasma TG levels and an approximately 10% increase in plasma HDL levels[29,30]. HMG-CoA reductase inhibitors appear equally effective in lowering LDL levels in patients with familial heterozygous hypercholesteroleniia, polygenic hypercholesterolemia, familial combined hyperlipidemia and other less characterized lipid disorders[31]. Bile acid binding resins such as cholestyramine and colestipolbindwithbile acids in the intestinal lumen and form insoluble complexes resulting in their decreased absorption from the ileum. This interrupts the enterohepatic circulation of bile acids and leads to their enhanced fecal excretion. In response to the depletion of bile acid pool, hepatic synthesis of bile acids from cholesterol is stimulated resulting ma decrease in the pool of intracellular cholesterol. This produces a compensatory increase in the expression of LDL receptors on hepatocytes which results in an enhanced clearance of LDL and a further decrease in plasma LDL levels[32]. Cholestyramine and cholestipol produce a 15-30% decrease in plasma LDL levels and have been found effective in patients with different genetic causes of primary hypercholesterolemia[31]. Majority of patients with primary hypercholesterolemia (except those with homozygous fanulial hypercholesterolemia) respond well toHMG-CoAreductase inhibitors orbile acid binding resins. In patients who respond poorly to one of these drugs or have profound elevation inLDL levels, itis sometimes necessary to combine both approaches. Studies have shown that a combination of HMG-CoA reductase inhibitorandbileacidbinding resinhave anadditive effectand 50-60% reduction in LDL levels is commonly achieved with this dual approach[33]. Probucol is generally considered a second line drug for the treatment of hypercholesterolemia. Probucol produces a 15-20% decrease in LDL levels and has no effect on TO levels[23]. It lowers LDL levels by enhancing its catabolism through the non- receptor mediated pathways and has no effect on rates of LDL production[23]. Probucol also has anti-oxidant properties and it retards the oxidation of lipoproteins[25] and thus it may be useful in the management of atherosclerosis. However, probucol decreases HDL levels by 20-25% by decreasing the synthesis of apo A-I and A-II and by increasing the activity of cholesterOl ester transfer protein[25]. This effect of probucol on HDL levels has limited its use in the management of patients with

hyperlipidemia.

B) High TG and normal LDL levels

An increase in plasma TO levels is usually due to an increased hepatic synthesis and secretion of VLDL particles. In some cases it could be due to a deficiency or abnormal function of lipoprotein lipase which results in a decreased clearance of TO- rich lipoproteins[13,14]. Majority of the cases of hypertriglyceridemia are due to secondary causes such as excessive dietary fat, increased intake of simple sugars, alcohol, obesity, pOorlycont.rolled diabetes mellilus, chronic renal failure and drugs like glucocorticoid, beta blockers or thiazide diuretics[8,13,14]. It is important to realize that primary and secondary causes of hypertriglyceridemia can co-exist and secondaiy causes can aggravate primary hypertriglyceridemia.

The treatment of elevated plasma TO levels is relatively straight forward. . Hypertriglyceridemias are usually very responsive to weight reduction and nutritional therapy consisting of avoidance of excessive dietary fats, simple sugars and alcohol[34]. If the patient is also diabetic; then plasma glucose levels must be controlled before any other therapy is undertaken. If the response to dietary therapy is not adequate, then drug therapy should be considered. Drug therapy should also be considered if the patient has severe hypertriglyceridemia (plasma TO levels greater than 800-1000 mg/dl) or has multiple risk factors[34]. Most of the hypertriglyceridemic patients readily respond to fibric acid derivatives(Gemfibrozil, Bezafibrate, Fenofibrate and Ciprofibrate) or nicotinic acid. Fibric acid derivatives lower plasma TO level by multiple mechanisms. They activate lipoprotein lipase resulting in enhanced catabolism of TO-rich lipoprOteins. They also produce a decrease in hepatic TG synthesis and VLDL secretion[35]. in addition to their effects on TO metabolism, fibrates also increase HDL levels by increasing the production of apoprotein A- 1. Studies have shown that fibrates lower plasma TO levels by 40- 50%, raise HDL levels by 15-30% and decrease LDL levels by 10- 15%[36]. Elevated TO levels have been shown to increase insulin production resulting in hyperinsulinemia and insulin resistance[37]. Elevated serum insulin concentration can further c hance TO synthesis and VLDL secretion resulting in a cyck' of hypertriglyceridemia and hyperinsulinemia[37]. Recent studies reveal that when TO levels are lowered with Gcmfibrozil, there is also a concurrent decrease in serum insulin levels[38]. Nicotinic acid or niacin is an effective drug for the treatment of both hypertriglyceridemia and hypercholestemlernia because of its favourable effect on the plasma concentrations of all lipoproteins. The daily requirement of nicotinic acid as vitamin is 15 rug whereas hypolipidernic effect is seen at doses over 1000 mg/day[25]. Nicotinic acid lowers lipoprotein levels by reducing hepatic VLDL production[39]. Since VLDL is partially converted to LDL, inhibition of VLDL production leads to a subsequent decrease in LDL levels. Nicotinic acid decreases production of apo B-l00 which is a marker for VLDL and LDL and increases the synthesis of apo A-i which is a marker for HDL. Therapeutic doses of nicotinic acid decrease plasma TO levels by 25-50%. raise HDL levels by 20- 25% and lower LDL levels by 20-30%[40]. Although nicotinic acid has favourable effects on all lipoproteins, many patients cannot tolerate it because of several adverse effects which include facial flushing, glucose intolerance, elevations in uric acid and hepatic transaminase levels[25]. Facial flushing is the most distressing symptom which is mediated by prostaglandin release andcanbeavoided by starting with a low dose and increasing the dose gradually, by the use of sustained release formulations or by the use of 325 mg aspirin 30 minute before taking nicotinic acid[34]. Glucose intolerance is another side-effect which limits its usefulness in diabetic patients with hyperlipidemia[34].

C) High LDL and high TG levels

Hyperlipidernic patients who have an elevation of both LDL and TO levels are among the most difficult to treat. They usually show a modest response to weight reduction and avoidance of dietary fat and cholesterol but often require drug therapy[23-25]. Nicotinic acid is the drug of first choice in these

patients because it decreases VLDL production and since majority of LDL is derived from VLDL, it also substantially lowers LDL levels[39]. Nicótinic acid has no effect on the catabolism of VLDL orLDL. Unfortunately one of the major cause for an increase in both LDL and TO levels is diabetes mellitus which may be aggravated by the use of nicotinic acid[34]. Fibric acid derivatives especially gemfibrozil has been used in many of the patients with elevated VLDL and LDL levels and it usually normalizes the TO levels, however, the elevated LDL level often persists[36]. Another alternative treatment is to combine fibric acid derivatives with an HMG-CoA reductase inhibitor. This combination has been shown to lower both plasma TG and LDL levels[41] however, there is an increased incidence of myositis and/or myopathy[41] which is a relatively rare side effect when these drugs are used alone. In some instances reversible rhabdomyolysis has also been reported with use of this combination[41]. Therefore, it is advisable to use this combination approach only in carefully selected patients. Creatine kinase levels should be measured prior to initiation of this combination therapy and eve rv two to three months during the therapy[25]. Clearly there is a need for additional agents that can lower both LDL and VLDL levels without producing the side effects associated with nicotinic acid or the combination of fibric acid derivatives and HMG-CoA reductase inhibitors.

D) Low HDL with normal or high TG and/or LDL

Low levels of HDL cholesterol may occur as an isolated biochemical abnormality with normal LDL and VLDL levels and is either familial or due to smoking, physical inactivity or therapy with androgens[42]. More commonly low HDL levels are accompanied by an increase in TO and/or LDL levels and are usually due to secondary factors such as hypertriglyceridernia, obesity and type II diabetes mellitus[13,14]. A decrease in HDL levels either alone or in combination with increased TG and LDL levels is usually associated with an increased risk of coronary heart disease[22]. The management of low HDL levels includes life style modifications and drug therapy. Patients should be advised to reduce caloric intake, maintain ideal body weight, abstain from smoking and exercise regularly[42]. Exercise not only helps in achieving the ideal body weight but it also increases insulin sensitivity, lowers serum TO levels and raises HDL levels[43]. In selected cases lipid lowering agents that may simultaneously raise HDL concentrations should be considered and the preferred drugs for this purpose include fibric acid derivatives and nicotinic acid[25]. Both fib'rntes and nicotinic acid increase the production of apo A-i which is the markerfor HDL[25,39]. Additionally, both of these drugs raise HDL level indirectly due to their VLDL lowering effect. VLDL normally exchanges its lipids with HDL, the TOs of VLDL move to HDL and cholesterol esters of HDL shift to VLDL. When VLDL levels is lowered, this exchange process is slowed and cholesteml esters rernainonHDL and thus HDL concentration is increased[35,39]. HMG-CoA reductase inhibitors have also been shown to produce a 8-10% increase in plasma HDL levels insome studies[29-31].

Use of traditional remedies in lowering plasma lipid levels

The plants have been a constant source of medicines throughout the development of civilization. The revival of interest in the natural products, pharmacology in the recent years is likely to provide cheaper and more effective drugs[44]. Several herbal remedies have been traditionally used to lower lipid levels, amongst which, garlic (Allium sativum) has been the extensively studied. Numerous studies both in experimental animals and in clinical trials have shown the usefulness of garlic 'in lowering plasma lipids[45-50]. Garlic also retards the oxidation of lipoproteins[49]. In addition to its multiple medicinal uses, garlic has also some effects that contribute to a lowering of the cardiovascular risk. These effects include reduction of blood pressure, inhibition of platelet aggregation, activation of fibrinolysis and reduction in plasma and blood viscosity[45,47]. Considering these effects, it is likely that garlic may be useful in the primaiy and secondaiy prevention of atherosclerosis. Several other plants have also been found to exhibit hypolipidemic effect. For example, a commonly used condiment, onion (Allium sepa)

is known to exert a lipid lowering effect[51]. Ginko bioloba is widely available in the form of a standardized extract and is primarily used for cerebral insufficiency due to aging[52] but it is also effective in lowering plasma lipids[53]. Some other plants, such as Gymnema sylvestra and Pterocarpus marsupium has been shown to be effective in lowering plasma lipids[54-56]. Recently a traditional recipe of Pakistan containing several different plant constituents including fruits of prunus bokharensis (Plum) and Berberis aristata (Zarshik) and the flowers of Nympaca lotus(Water lily) and Rosa indica (White rose) was studied by a research team at the Ayub Medical College, Abbottabad[57] and it was found to have lipid lowering effect. Interestingly, one plant (Berberis anstata) of this recipe was also found to have a hepatoprotective effect in a recent study in our lab[58]. Hyperlipidemia is usually accompanied by several other cardiovascular disorders such as hypertension and ischemic heart disease. It is quite common that patients receive multiple drugs in addition to the anti-hyperlipidemic therapy. Therefore, in such cases, the characteristics of these drugs should be taken into account. Beta-adrenoceptor blockers have been extensively used in the treatment of hypertension and ischemic heart disease whereas, thiazide diuretics are widely used in the management of hypertension. Both classes of drugs have been shown to disturb the lipid profile[8] which may negate their useful effects on cardiovascular system. On the other hand, calcium ‘channel blockers which are also widely used in hypertension and ischemic heart diseases are devoid of such side-effects. Rather, they have been shown to have a beneficial effect by lowering plasma lipid levels[59]. Interestingly, calcium channel blockers are abundantly present in medicinal plants. Recently we have shown that several plants, ‘which have been traditionally used to treat hypertension, contain calcium channel blocker like substances[60-65]. Such examples include Artemisia scoparia (Jhan), Artemesia absinthiuni (Afsanteen), Cyperus scariosus (Nagar motha), Cuscuta reflexa (Akasbel), Daucus carota (Carrot), Moringa oleifera (Sohajnan) and Rubia cordifolia (Manjit) Thus, it is possible that these plants may also have lipid lowering properties and hence need tobe studied furtherfor this activity. Pakistan is rich in the herbal wealth and well over 70% of country\'s population rely on traditional remedies which mainly consists of plant constituents[66]. However, these remedies have not been tested scientifically because of the lack of proper expertise and there is a great potential for working in this field.

Conclusion

High LDL and low HDL levels are major risk factors for coronaty heart disease whereas, hypertnglyceridemia in combination with low HDL or high LDL predisposes to enhanced atherogenesis. Nutritional counselling and drug therapy for hyperlipidemia can significantly decrease cardiovascular mortality and morbidity. The drug therapy in patients with hyperlipidemia should be individualized with careful consideration of secondary causes and other risk factors, plasma lipoprotein profile, patient’s life style, anticipated side-effects, desired benefits and cost- effectiveness. The patients should be encouraged to quit smoking, improve their dietary habits, attain ideal body weight and participate in appropriate exercise programmes. Serum lipid levels should be regularly monitored and an effort should be made to control hypertension, diabetes and other associated diseases in these patients. While the major focus of our physicians is on allopathic medicines, it should be borne in mind that a substantial proportion of ourpatient population use traditional remedies, which should not be ignored.

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