Management of hyperlipidemias: An update

Nitin Ranjan

Department of Dermatology, Jawaharlal Nehru Medical College, Aligarh Muslim University, Aligarh, India

Address for correspondence:
Dr. Nitin Ranjan, Department of Dermatology, Jawaharlal Nehru Medical College, Aligarh Muslim University (AMU), Aligarh - 202 001, Uttar Pradesh, India. E-mail: drnitinranjan@gmail.com

ABSTRACT

The discovery of the key enzymes, receptors, and transporters in cholesterol biosynthesis has enabled us to assemble fragments of knowledge concerning lipids and lipoproteins into dynamic pathways, leading to the development of a multitude of lipid-lowering drugs. After a brief recapitulation of the pathways of cholesterol metabolism and the dermatologic manifestations of lipid derangement, we shall review drugs which modify intestinal cholesterol and bile-acid reabsorption, and hepatic lipoprotein biosynthesis and catabolism. The current literature is examined to determine future therapeutic targets in lipid metabolism, as well as the role of traditional foods as lipid-lowering agents. The latest National Cholesterol Education Program guidelines for managing hypercholesterolemia are also discussed.

Key words: Guidelines, Lipid metabolism, Low-density lipoprotein cholesterol, Statins

INTRODUCTION

Cholesterol serves not only as an essential component of the cell membrane but also as the precursor molecule from which steroid hormones, bile salts, and vitamin D are synthesized. It is both derived from the diet and synthesized within the body, mainly in the liver. Cholesterol circulates as a component of lipoproteins. The principal plasma lipoproteins are the chylomicrons (CMs), very low density lipoproteins (VLDL), low-density lipoproteins (LDL), and high-density lipoproteins (HDL). The principal fat in the diet is the triglycerides (TG), which are absorbed in the intestine. The lipoproteins are transported in combination with apoproteins (apo), like apo-A, apo-B, and apo-C.

THE PATHWAYS

Transport of lipoproteins can be divided into:

Exogenous transport
From ingested food to intestine to peripheral cells and liver [Figure 1]
Products of fat digestion from the gut (cholesterol, TG) are packaged with intestinal apo-B48 to form nascent CMs. This process is mediated by microsomal triglyceride transfer protein (MTP).[1] In the circulation,

nascent CMs acquire cholesteryl esters (ChE), apo-C, and apo-E from HDL to form CMs. These CMs come in contact with lipoprotein lipase (LPL) located on the luminal surface of vascular endothelium of skeletal muscle and adipose tissue. LPL breaks down the triglyceride component of CMs into free fatty acids (FFA) and monoglycerides, in the process converting the CMs to smaller particles called CM remnants. The cholesterol-rich CM remnants are taken up by the liver via LDL-receptor-like-protein (LRP) receptors or Apo-E receptors.[2] In this way, dietary cholesterol finally reaches the liver.

Endogenous transport
From liver to peripheral tissues: the apo-B100 lipoprotein system [Figure 2]
Analogous to the secretion of nascent CMs by the gut, liver synthesizes and secretes nascent VLDL, by complexing TG and apo-B100 under the mediation of MTP.[1] Triglyceride-rich nascent VLDL serves as an efficient acceptor of ChE from HDL. This transfer takes place under the agency of cholesteryl ester transfer protein (CETP) in the plasma and leads to the formation of mature VLDL.[3] During circulation, LPL hydrolyses the TG of VLDL to FFA and monoglycerides, in the process converting VLDL to smaller lipoproteins called intermediate density lipoproteins (IDL), and further to still smaller ChE-rich LDL. LDL supplies tissues with
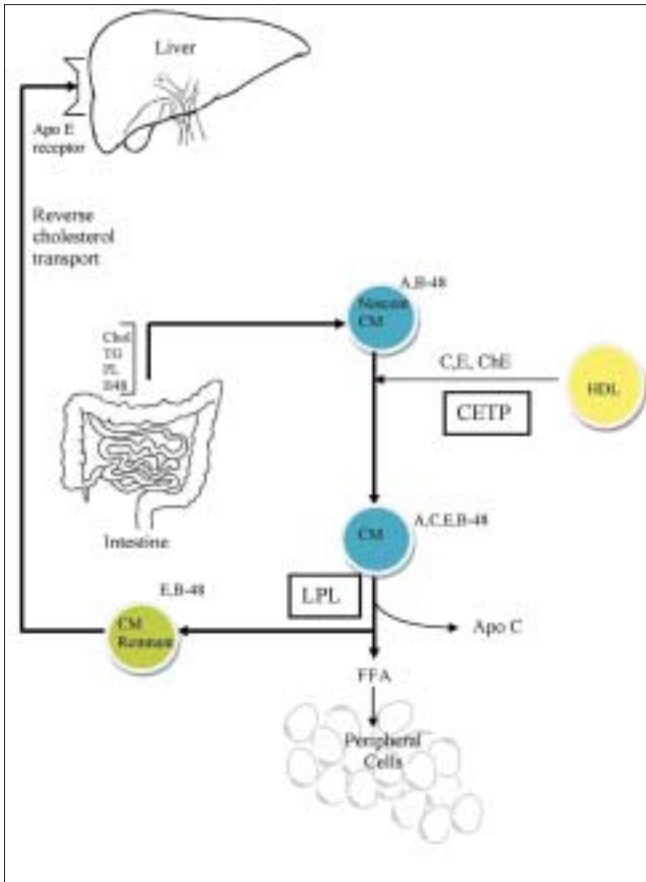
Figure 1: Exogenous transport in chylomicrons (chylomicron pathway) (Apo E: apoprotein E, chol: cholesterol, TG: triglycerides, PL: phospholipids, B-48: apoprotein B48, A: apoprotein A, CM: chylomicron, C: apoprotein C, E: apoprotein E, ChE: cholesteryl esters, CETP: cholesteryl ester transfer protein, HDL: high-density lipoproteins, LPL: lipoprotein lipase, Apo C: apoprotein C, FFA: free fatty acids)

Figure 2: Endogenous transport from the liver (VLDL-LDL pathway) (LDL: low-density lipoproteins, B-100: apoprotein B100, C: apoprotein C, E: apoprotein E, HTGL: hepatic triglyceride lipase, IDL: intermediate-density lipoproteins, LPL: lipoprotein lipase, FFA: free fatty acids, VLDL: very low density lipoproteins, ChE: cholesteryl esters, CETP: cholesteryl ester transfer protein, HDL: high-density lipoproteins, chol: cholesterol, TG: triglycerides)

cholesterol. Thus the liver serves as the major site for both cholesterol synthesis and LDL catabolism.

From peripheral tissues to liver: the apo-A$_1$ lipoprotein system [Figure 3]

Nascent HDL particles are synthesized by apolipoprotein-phospholipid complexes in plasma, and also by intestine and the liver. Peripheral tissues (including liver) transfer unesterified cholesterol to nascent HDL by the membrane protein ATP-binding cassette protein A1 (ABCA1).[4] Lecithin-cholesterol acyltransferase (LCAT), an enzyme present on HDL, esterifies this cholesterol, leading to the formation of ChE. VLDL and CMs transfer TG to nascent HDL, which leads to formation of mature HDL. HDL is taken up directly by hepatocytes via the scavenger receptor class BI (SR-BI).[5] The transfer of excess cholesterol from the tissues back to the liver via HDL is called 'reverse cholesterol transport.'
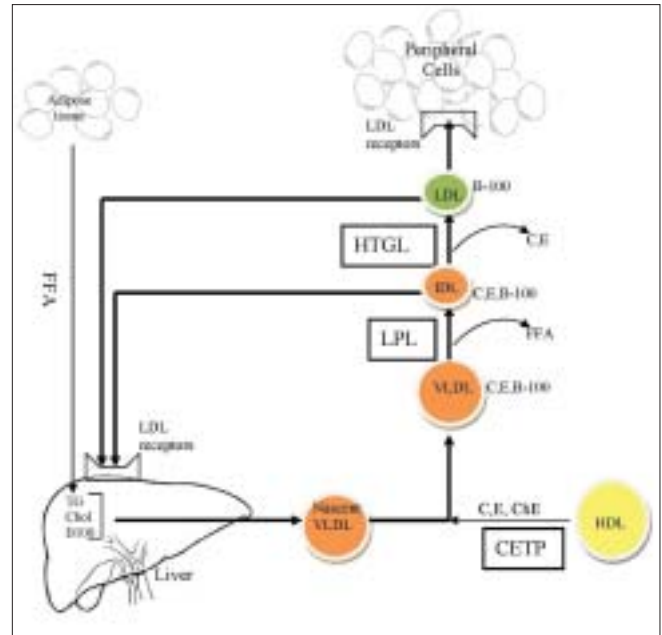
HYPERLIPIDEMIAS

Hyperlipidemias are classified as primary or secondary. Patients with primary hyperlipidemia have been classified into 5 major groups according to plasma lipoprotein patterns [Table 1, Figure 4].[6,7] Conditions causing secondary hyperlipidemia include obstructive liver disease, various hematopoietic diseases (myeloma, Waldenstrom's macroglobulinemia, cryoglobulinemia, hemochromatosis), chronic renal failure, myxedema, pancreatitis, and drugs like estrogens, corticosteroids, and retinoids.[8]

DERMATOLOGIC MARKERS OF LIPID DERANGEMENT

Abnormalities of lipid metabolism may favor lipid deposition in the skin and present as xanthomas.[9] Xanthelasma palpebrarum is the commonest type of cutaneous xanthoma and typically involves the upper eyelids as symmetrical, soft, yellowish papules and plaques near the medial canthi.[10,11] The major lipid stored in xanthomas is esterified cholesterol.[12,13] Xanthelasma is a marker of dyslipidemia, requiring a complete lipid profile to detect patients potentially at increased risk of cardiovascular disease.[14] However,

WHO	New names	Etiology	Lipoproteins	Onset (years)	Skin manifestations
Table 1: Genetic primary hyperlipidemias					
I	Chylomicronemia syndrome	Lipoprotein lipase deficiency	CM	Child	Eruptive / tuberoeruptive xanthomas
		Apo C II deficiency			Other: recurrent pain abdo, acute relapsing pancreatitis
IIa	Familial hypercholestrolemia	Abnormality in LDL receptor l/t decrease in LDL catabolism	LDL	20-40 (heterozygous)	Heterozygotes: Tendinous xanthomas
				0-1 (homozygous)	Homozygotes: Tendinous and tuberous xanthomas, xanthelasma
IIb	Familial combined hypercholestrolemia	Increased production of VLDL (± LDL)	LDL VLDL	20-30	Xanthomas and xanthelasmas are less common
		Decreased catabolism of VLDL, LDL			
III	Dysbetalipoproteinemia	No uptake of CM remnants and IDL by the liver	CM IDL	10-30	Tuberous, tuberoeruptive, plane xanthomas (palmar and digital creases)
		(Particles containing Apo E 2 show no binding to Apo B/E receptors)			Eruptive xanthomas (over elbows, knees, wrist)
IV	Familial pure hypertriglyceridemia	Increased VLDL triglyceride synthesis	VLDL	20-40	Xanthomas not a usual feature
		Increased VLDL apo-B synthesis			During exacerbations: Eruptive xanthomas (over buttocks, arms)
		Decreased catabolism			
V	Familial combined hypertriglyceridemia	Features of both type IV and type I	CM VLDL	20-40	Eruptive xanthomas are typical of type V
					Other: pain abdo, HSM, lipemia retinalis

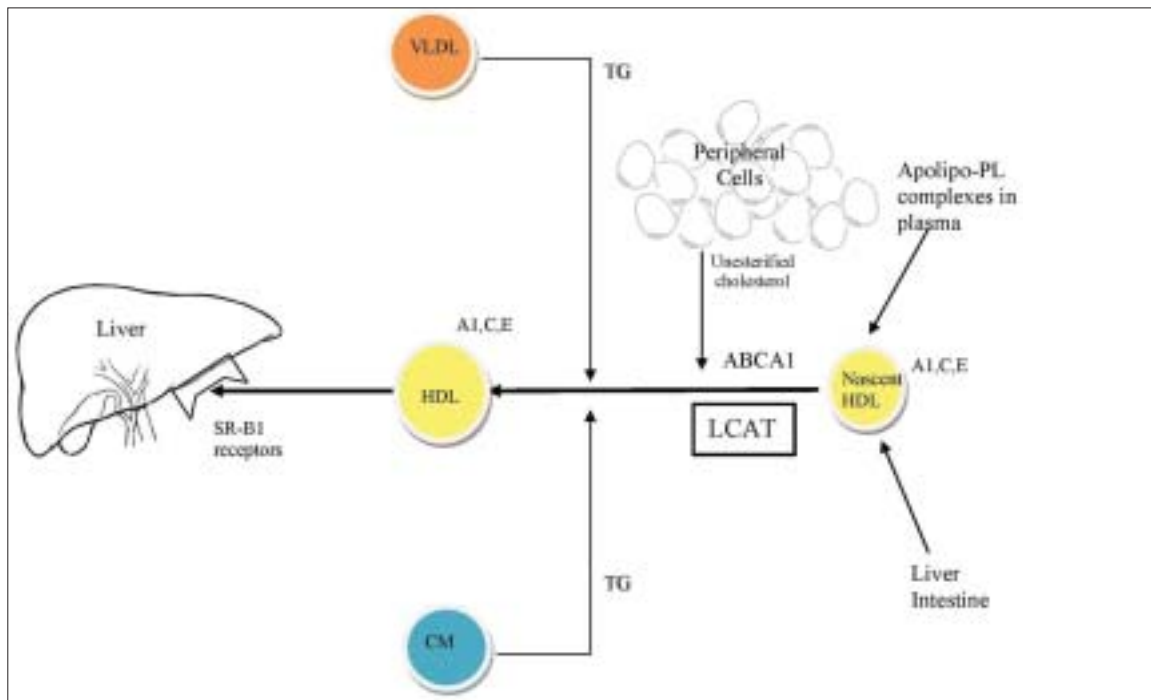abdo - abdomen, HSM - hepatosplenomegaly

Figure 3: Endogenous transport of lipids from tissues to liver (reverse cholesterol transport) (VLDL: very low density lipoproteins, TG: triglycerides, apolipo-PL: apolipoprotein-phospholipid complex, A1: apoprotein A₁, C: apoprotein C, E: apoprotein E, HDL: high-density lipoproteins, ABCA1: ATP-binding cassette A1, LCAT: lecithin-cholesterol acyltransferase, CM: chylomicron, SR-B1: scavenger receptor class BI)
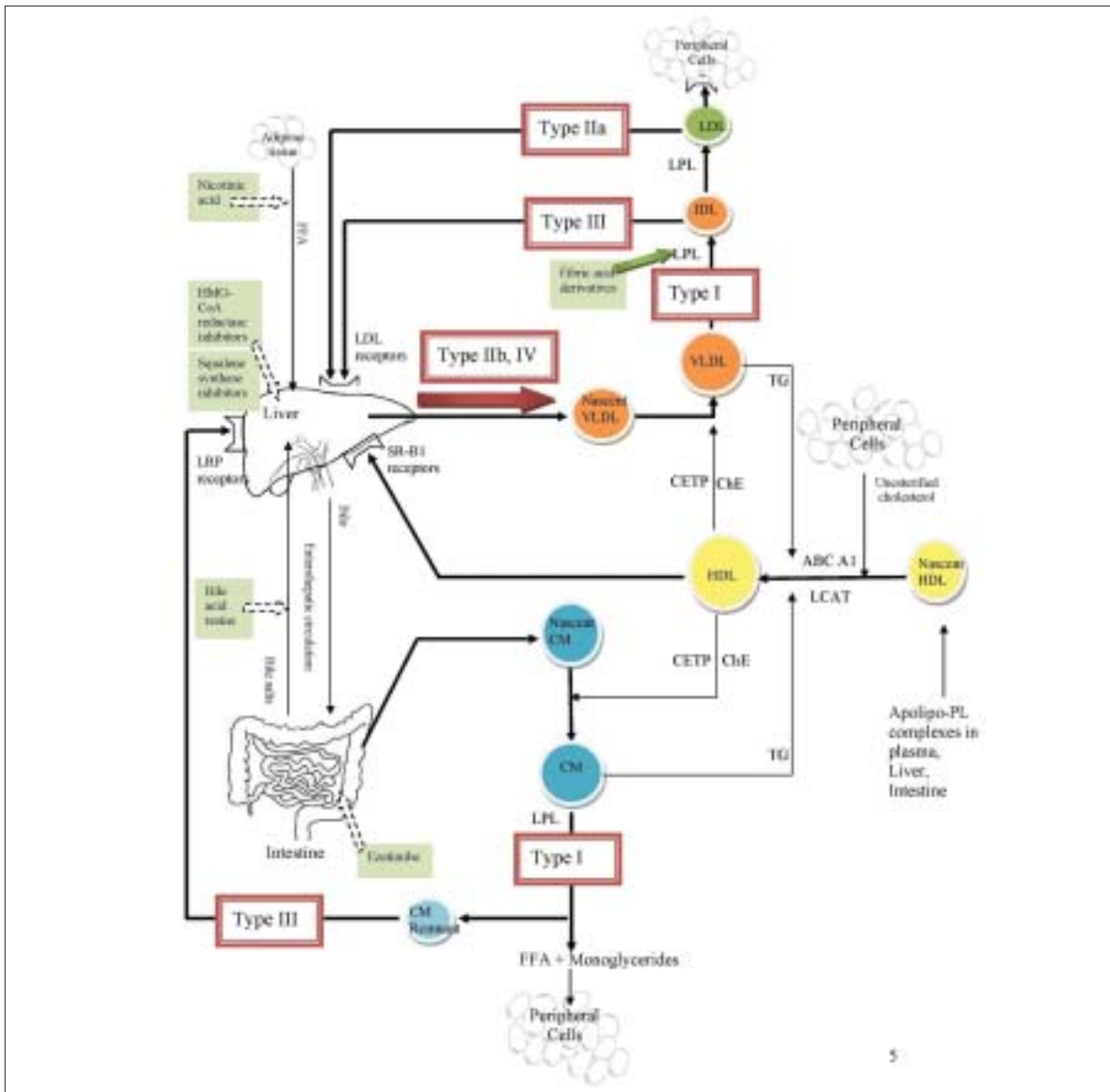
Figure 4: Overview of lipid transport, genetic primary hyperlipidemias, and sites of action of lipid-lowering drugs (LDL: low-density lipoproteins, LPL: lipoprotein lipase, IDL: intermediate-density lipoproteins, VLDL: very low density lipoproteins, TG: triglycerides, ChE: cholesteryl esters, CETP: cholesteryl ester transfer protein, HDL: high-density lipoproteins, ABCA1: ATP-binding cassette A1, LCAT: lecithin-cholesterol acyltransferase, CM: chylomicron, LPL: lipoprotein lipase, FFA: free fatty acids, LRP: LDL-like receptors) Note: Dashed arrows represent inhibition of the pathway, bold arrows represent stimulation of the pathway, boxes indicate type of primary hyperlipidemia

only about half of the patients with xanthelasma are hyperlipidemic.[15] The most frequent hyperlipidemia associated with xanthelasma is type IIa.[16] Less frequently, types IIb, III, and IV are found.[16] Isolated xanthelasmata are often treated with destructive modalities, like trichloroacetic acid, electrocautery, surgical excision,[17] carbon dioxide laser,[18] pulsed dye laser,[19] and erbium:YAG laser.[20] A brief review of various other types of xanthomas is presented in Table 2.

MANAGEMENT

Traditional foods and herbal therapies

Dietary advice has a small but significant role to play in normalizing abnormal serum lipids in those at high risk of cardiovascular disease, and reductions in serum total cholesterol levels of the order of 3% to 6% are to be expected.[21,22] Replacement of saturated fats by unsaturated fats leads to improved lipid levels.[23] However, it is not clear whether

Table 2: Disorders of lipid storage			
Type of xanthoma	**Lesions**	**Sites**	**Disorders**
Tuberous xanthoma	• Small yellow/orange firm papules (0.5 cm) to lobulated tumours (≥2.5 cm) • Larger lesions tender on direct pressure	• Pressure areas like extensors of limbs e.g. (knees, elbows, buttocks)	• Type IIa, III, IV • Hypothyoidism, primary biliary cirrhosis (PBC), myasthenia gravis (MG)
Tendinous xanthoma	• Slowly enlarging subcutaneous nodules attached to tendons, ligaments, fascia, periosteum • Asymptomatic	• Extensor tendons of hands and feet • Achilles tendon	• Type IIa • Prolonged cholestasis
Eruptive xanthoma	• Pinhead or larger yellow papules with a reddish base • Fleeting • sometimes pruritic	• Buttocks, shoulders, extremities	• Type I, IV, V • Diabetes mellitus
Plane xanthoma	Yellow or orange macules or slightly palpable plaques	• Any site • Xanthoma Palmaris pathognomonic of type III	• Type III • PBC, MG
Generalised plane xanthoma	Diffuse plane xanthomas	• Face, neck, thorax • Also: flexures, palms	• MG • Endogenous hypertriglyceridemia

polyunsaturated or monounsaturated fats are most cardioprotective.[24] Rapeseed oil, which is rich in omega-3 fats, is especially useful.[25] Soluble fiber (in oats, pectin, psyllium, guar gum) results in a significant but very modest lipid-lowering effect.[26-28] Unrealistic (47g per day) intake of purified soy protein will lower total cholesterol levels by about 0.6 mmol L.[29] A recent review of the efficacy of garlic as an antihyperlipidemic agent found it difficult to recommend garlic as an antihyperlipidemic agent owing to the low methodological quality of the studies.[30] Stanol esters and plant sterols reduce cholesterol in those on an average diet, but may lack efficacy in those already on a low fat diet.[25]

Drug treatment
Statins
One of the major advances in the management of hyperlipidemias has been the development of the statins, derived initially from fungi and later as purely synthetic molecules.[31-33] The statins are competitive inhibitors of 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase, the rate-limiting enzyme in cholesterol biosynthesis. Inhibition of HMG-CoA reductase leads to a decrease in intrahepatic cholesterol concentration, to which the liver responds by inducing its LDL receptors, leading to an increase in receptor-mediated LDL catabolism.[32]

Vis-à-vis the induction of LDL receptors, the SR-B1 receptors also increase their uptake of cholesterol from HDL.[34] However, the statins also decrease the activity of CETP.[35,36] Thus the overall effect is a small increment in HDL.[34]

Statins decrease serum triglycerides.[37] Statin-induced increased LDL-receptor activity also leads to the enhanced removal of the TG-rich lipoproteins VLDL and IDL. Similarly, increased activity of LDL receptor leads to enhanced uptake of CM remnants, thereby increasing postprandial TG clearance.

Five statins are currently available [Table 3].[38] Out of these, rosuvastatin and atorvastatin are the most potent.[39]

However, another response to statin-induced decrease in intrahepatic cholesterol is the increased expression of sterol regulatory element–binding proteins (SREBP).[40] This leads to increased synthesis of HMG-CoA reductase, essentially an attempt by the body at maintaining metabolic homeostasis. But this imposes a pharmacologic limitation on the amount of LDL lowering, which can be achieved by treatment with HMG-CoA reductase inhibitors. Development of noncompetitive inhibitors of HMG-CoA reductase, like apomine, is the solution.[41]

Bile-acid sequestrating agents (BASA)
BASA are anion exchange resins, which bind bile acids

Table 3: Lipid-lowering agents[38]				
Drugs	Mechanism of action and effects on lipoproteins	Use	Adverse effects	Contraindications
HMG-CoA reductase inhibitors Lovastatin (20-80 mg) Pravastatin (20-40 mg) Simvastatin (20-80 mg) Fluvastatin (20-80 mg) Atorvastatin (10-80 mg)	By inhibiting conversion of HMG-CoA to mevalonate LDL decreased 18-55% HDL increased 5-15% TG decreased 7-30%	Type IIa	SGOT,SGPT Myositis Lens opacity	Absolute: acute or chronic liver disease Relative: concomitant use with certain drugs
Bile acid sequestrants Cholestyramine (4-16 g) Colestipol (5-20 g) Colesevelam (2.6-3.8 g)	By interrupting enterohepatic recycling of bile acids LDL decreased 15-30% HDL increased 3-5% TG No change or increase	Type IIa	Constipation and bloating Hemorrhoidal bleeding Dry flaking skin Binds digoxin, warfarin, statins	Absolute: Dysbetalipoproteinemia TG > 400 mg/dl Relative: TG > 200 mg/dl
Nicotinic acid Immediate release (crystalline) nicotinic acid (1.5-3 gm) Extended release nicotinic acid (Niaspan®) (1-2 g) Sustained release nicotinic acid (1-2 g)	By decreasing the flux of FFA to the liver LDL decreased 5-25% HDL increased 15-35% TG decreased 20-50%	Type IIa Type IV	Flushing SGOT, SGPT Tachycardia, arrhythmias Pruritus Glucose intolerance Hyperuricemia Nausea, diarrhea	Absolute: Chronic liver disease, Severe gout Relative: Diabetes, Hyperuricemia, Peptic ulcer disease
Fibric acid derivatives Gemfibrozil (600 mg BID) Fenofibrate (200 mg) Clofibrate (1000 mg BID)	Increased lipolysis of triglyceride via LPL LDL decreased 5-20% HDL increased 10-20% TG decreased 20-50%	Type III Type IV	SGOT, SGPT Gallstones Myositis Arrhythmias Anticoagulant activity of warfarin	Absolute: Severe renal disease, Severe hepatic disease

in the intestinal lumen. The physiological process of enterohepatic circulation involves reabsorption of bile acids in the terminal ileum and their circulation back to the liver.[42] BASA bind the bile acids, thus impeding their reabsorption and significantly increasing their fecal excretion. In response, the liver steps up the synthesis of bile acids from cholesterol. This leads to the depletion of intrahepatic cholesterol, which causes increased expression of LDL receptors.[43] Hepatic LDL uptake is thereby raised, and the net result is a decrease in LDL. BASA promote apo-A1 synthesis by an unknown mechanism and tend to raise HDL levels.[44]

Three BASA are currently available [Table 3]. Their use has been hindered by inconvenient dosing and by unpleasant side effects (e.g., constipation).[45] However, colesevelam appears to be better tolerated than the older resins.[46,47] BASA nonspecifically bind anions and interfere with absorption of a number of drugs which are anionic at intestinal pH (statins, fenofibrate,

corticosteroids, diuretics, tricyclic antidepressants, nonsteroidal anti-inflammatory drugs, thyroxine, and digoxin). These drugs should be administered at least 4 hours after or 1 hour before the last dose of BASA.[48] As BASA tend to raise triglycerides, they are contraindicated in patients with hypertriglyceridemia (>400 mg/dL).[49]

Nicotinic acid (NA)

Plasma FFA are immediate precursors of hepatic and subsequently plasma triglycerides transported in VLDL. NA is immediately taken up by adipose tissue via a specific high-affinity G-protein–coupled receptor.[50] It then inhibits lipolysis in adipose tissue, resulting in a decrease in plasma FFA. NA, in a dose-dependent way, lowers triglyceride-rich VLDL and cholesterol-rich LDL.[51] Furthermore, NA is the most potent HDL-raising drug.[52] But the unpleasant side effect of flushing precludes many patients from taking this drug.[53]

Three formulations of NA are currently available [Table 3]. Of these, the prolonged-release (PR) preparation,[54] also called extended-release (ER) preparation, has absorption rates between those of IR (immediate-release) and SR (sustained-release) preparations, and a lesser frequency and intensity of causing flush.[55]

Fibric acid derivatives (fibrates)

The lipid-modifying effects of fibrates are largely mediated by their ability to activate peroxisome proliferator–activated receptors (PPARs).[56] PPARs are ligand-activated transcription factors that control gene expression by interacting with response elements located upstream. PPARα is expressed primarily in the liver and brown adipose tissue. PPARα controls a number of genes involved in lipid metabolism, including those encoding for apo-CIII, apo-AI, and apo-AII.[57] Fibrates reduce triglycerides through PPARα-mediated reduced expression of apo-CIII, which serves as an inhibitor of lipolytic processing and receptor-mediated clearance. This leads to increased LPL synthesis and enhanced clearance of triglyceride-rich lipoproteins. Fibrate-mediated increases in HDL are due to PPARα stimulation of apo-AI and apo-AII expression.[58]

Three fibric acid derivatives are currently available [Table 3]. Fibrates are primarily used for lowering elevated triglycerides because the LDL cholesterol–lowering effects of fibrates are generally only 10% or less in persons with hypercholesterolemia.[38] Fenofibrate, however, reduces LDL cholesterol by a relatively greater extent than gemfibrozil.[59]

Other therapeutic targets in lipid metabolism

Guggulsterone (gugulipid) is a widely used yet controversial hypolipidemic drug. The plant sterols E- and Z-guggulsterone are the active compounds[60] derived from the gum resin of the mukul myrrh tree (Commiphora mukul). They act as antihyperlipidemic agents via the antagonism of the Farnesoid X receptor (FXR)[61,62] and up-regulation of the bile salt export pump (BSEP).[63] E- and Z-guggulsterone are currently marketed under the brand name Gugulipid. Most of the clinical trials conducted in Asia demonstrated hypolipidemic activity of gugulipid with an average decrease of 10%-30% and 10%-20% in total cholesterol and triglyceride respectively.[63] However, the first and only clinical trial conducted in the U.S. population found that gugulipid did not improve the levels of serum cholesterol and might in fact raise LDL levels.[64] A recent review concluded that at present, there is not enough scientific evidence to support the use of guggul for any medical condition.[65] Larger clinical trials are required to obtain extensive clinical knowledge of this drug.

A number of lipid-lowering pharmacological agents are currently under evaluation [Table 4].[66,67] The most promising among these are ezetimibe[68] and squalene synthase inhibitors.[69]

Ezetimibe blocks uptake of cholesterol into jejunal enterocytes, hence selectively blocking dietary and biliary cholesterol absorption from the gut. It acts by decreasing the intestinal cholesterol supply to the liver, lowering hepatic cholesterol levels and thus inducing LDL receptor expression.[70] Unlike the bile-acid sequestrants, it does not interfere with absorption of fat-soluble drugs. Moreover, ezetimibe does not increase serum TG.[71]

Squalene synthase (SS) is the first enzyme in the hepatic cholesterol biosynthetic pathway which produces a metabolite (lanosterol) committed to cholesterol synthesis.[72] The result of inhibition of SS is analogous to that of HMG-CoA reductase. Induction of LDL receptors occurs, leading to a decrease in circulating LDL. Thus SS inhibitors act similar to statins, albeit at a different and a more specificlevel.[72]

Table 4: Newer lipid-lowering drugs

Target	Drug	Use
Bile acid resorption	Apical bile acid transport inhibitors	LDL reduction
Cholesterol absorption	Ezetimibe	LDL reduction
Cholesterol transfer	CETP inhibitors or vaccines	HDL increase
HDL production	ABC-A1 up-regulators	HDL increase
Lipolysis	New PPAR agonists, fibrates	VLDL reduction
Lipoprotein catabolism	New statins	LDL reduction
Lipoprotein production	Microsomal transport protein inhibitors	VLDL reduction
Reverse cholesterol transport	Apo A/phospholipid infusions	Atheroma regression

Table 5: LDL cholesterol goals and levels for TLC and drug therapy in various risk categories

Risk category	LDL Goal	LDL level at which to initiate TLC	LDL level at which to consider drug therapy
CHD or CHD risk equivalents	< 100 mg/dl	≥ 100 mg/dl	≥ 130 mg/dl
2+ Risk factors	< 130 mg/dl	≥ 130 mg/dl	10-year risk 10-20%: >130 mg/dL 10-year risk <10%: >160 mg/dL
0 -1 Risk factors	< 160 mg/dl	≥ 160 mg/dl	≥ 190 mg/dl

NCEP GUIDELINES

The NCEP Adult Treatment Panel (ATP) first published guidelines for managing hypercholesterolemia in 1988 (ATP I)[73] and revised them in 1993 (ATP 2).[74] The latest NCEP report (ATP III) has been published in 2001.[38]

The first step is to determine lipoprotein levels after a 9- to 12-hour fast.[38] Next, coronary heart disease (CHD) risk equivalents and major risk factors should be established. CHD risk equivalents include clinical CHD, symptomatic carotid artery disease, peripheral arterial disease, abdominal aortic aneurysm, and diabetes. Major risk factors (exclusive of LDL cholesterol) include cigarette smoking, hypertension, low HDL cholesterol (<40 mg/dL), family history of premature CHD, and age (men >45 years; women >55 years). CHD risk equivalents and risk factors are then used to determine the risk category of the patient [Table 5].

Therapeutic lifestyle changes (TLC)[38] are considered first-line therapy in the management of high cholesterol. A 3-month trial of TLC should precede the use of drug therapy. The essential features of TLC are (a) reduced intake of saturated fats [less than 7% of total calories] and cholesterol [less than 200 mg/d]; (b) therapeutic options for enhancing LDL lowering — such as plant stanols/sterols [2 g/d] and increased soluble fiber [10-25 g/d; (c) weight reduction; and (d) increased physical activity.

According to ATP III, the most cost-effective approach to prevention of CHD is: diet modification, exercise, and weight control, combined with avoidance or cessation of smoking. Cigarette smoking is a strong, independent risk factor for CHD and leads to elevated triglycerides and low HDL levels. Smoking cessation should receive prime emphasis in the clinical strategy to reduce CHD risk. While moderate intakes of alcohol in middle-aged and older adults may reduce risk for

CHD, high intakes of alcohol produce multiple adverse effects. No more than 2 drinks per day for men and no more than 1 drink per day for women should be consumed. Persons who do not drink should not be encouraged to initiate regular alcohol consumption. Physical activity as a component of TLC includes enough moderate exercise to expend at least 200 kcal per day. Thus life-habit changes — weight control, exercise, and smoking cessation — will favorably modify multiple risk factors, including elevated triglycerides and low HDL levels.

However, for patients with CHD or CHD risk equivalents and an LDL cholesterol level of 130 mg/dL or higher, an LDL-lowering drug may be started simultaneously with TLC to achieve the LDL goal of less than 100 mg/dL.

The NCEP recommends the use of statins as first-line therapy when LDL cholesterol–lowering drugs are indicated. BASA's LDL-lowering effects may be enhanced in combination with other cholesterol-lowering medications, particularly statins. Nicotinic acid is recommended for high-risk patients with low levels of LDL cholesterol, high triglycerides, and low HDL cholesterol — a triad known as atherogenic dyslipidemia.[38] Fibrates are primarily used for persons with very high triglycerides to reduce risk for acute pancreatitis and for those with dysbetalipoproteinemia.

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Multiple Choice Questions

1. Microsomal triglyceride transfer protein helps in the synthesis of:
   a. Nascent chylomicrons
   b. Nascent VLDL
   c. Both of the above
   d. None of the above

2. Lecithin-cholesterol acyltransferase is present on:
   a. VLDL
   b. IDL
   c. LDL
   d. HDL

3. Scavenger receptor class BI helps in the uptake of:
   a. VLDL
   b. IDL
   c. LDL
   d. HDL

4. What percentage of patients having xanthelasma are hyperlipidemic?
   a. 7%
   b. 25%
   c. 50%
   d. 93%

5. Which is the most frequent hyperlipidemia found in patients having xanthelasma?
   a. Type I
   b. Type IIa
   c. Type IIb
   d. Type III

6. Which of the following statins is the most potent?
   a. Lovastatin
   b. Pravastatin
   c. Simvastatin
   d. Atorvastatin

7. Which statement about bile-acid sequestrating agents (BASA) is not true:
   a. BASA decrease LDL
   b. BASA decrease triglycerides
   c. BASA increase HDL
   d. BASA increase Apo-A1 synthesis

8. Which of the following formulation of nicotinic acid has the least frequency and intensity of causing flushing?
   a. Prolonged-release
   b. Immediate-release
   c. Sustained-release
   d. All are equal

9. Fibrates act as lipid-lowering agents by activating:
   a. PPARα
   b. PPARβ
   c. PPARγ
   d. PPARδ

10. According to the latest NCEP guidelines, what is the optimal level of LDL cholesterol?
    a. < 100 mg/dl
    b. < 130 mg/dl
    c. < 150 mg/dl
    d. < 160 mg/dl

Answers
1. c, 2. d, 3. d, 4. c, 5. b, 6. d, 7. b, 8. a, 9. a, 10. a