



## Dyslipidemia Management

Management of dyslipidemia is essential to the prevention and treatment of atherosclerosis. High levels of low-density lipoprotein cholesterol (LDL-C), low levels of high-density lipoprotein cholesterol (HDL-C), and high levels of triglycerides increase the risk of developing this condition. This chapter will review normal lipid profiles, lipid pathways, and lipid subclasses. In addition, treatment guidelines and drug and lifestyle therapies will be presented. The Adult Treatment Panel III (ATP III) report contains the National Cholesterol Education Program's (NCEP) evidence-based clinical guidelines for lipid testing and management. This chapter presents screening guidelines for coronary heart disease (CHD) risk and the metabolic syndrome, the ATP III guidelines for primary and secondary prevention of atherosclerosis, and the implications of dyslipidemia management for nursing practice. A new set of guidelines is due for publication in 2010 so check the National Heart Lung and Blood Institute Web site (<http://www.nhlbi.nih.gov/index.htm>) for the ATP IV report in the future.

### **UNDERSTANDING LIPOPROTEIN STRUCTURE, FUNCTION, AND METABOLISM**

- Structure of lipids includes
  - Core composed of cholesterol ester and triglyceride (TG)
  - Coat containing apoproteins A, B, C, E, J, and Apo(a); unesterified cholesterol; and phospholipids

- Cholesterol is an important component of cell walls and needed throughout the body for cell stability and regeneration of all forms of tissues.
- Cholesterol is defined based on size of molecules, density, protein content, and major apoproteins. Table 10–1 describes the various forms of lipoproteins.
  - Chylomicrons rapidly enter the plasma from the gut after meals. This is the largest but least dense molecule. It is triglyceride rich.
  - Very low density lipoproteins (VLDL) serve the role of providing a source of triglyceride when fat is not readily available from the diet. The liver can secrete VLDL that is not quite as large but is slightly more dense than chylomicrons. Through several metabolic processes the VLDL is converted to Intermediate density lipoprotein (IDL) and eventually to low density lipoproteins (LDL). As these processes occur, the triglyceride content of the lipid molecule decreases and cholesterol increases. The overall size decreases but the molecule becomes more dense.
  - LDL molecules are usually 4% to 8% triglyceride content but this can increase when there is a higher level of serum triglycerides. LDL particles serve as the major carrier of cholesterol to the body tissues for cell membrane use. LDL-C level has the greatest strength of all the lipid particles for predicting CHD.
  - High-density lipoprotein (HDL) level is inversely related to development of CHD, theorized to result from reverse cholesterol transport (transport of cholesterol from the tissue to the liver). High HDL is protective for the development of CHD.
  - Not all LDL and HDL is the same in terms of structure and function. New information on the subclasses of the various lipoproteins and which ones are more specific to CHD risk will be discussed later in this chapter.

**Table 10–1. Plasma Lipoprotein Composition**

	Origin	Density (g/mL)	Size (nm)	% Protein	Apoprotein Major (Minor)
Chylomicrons	Intestines	< 0.95	100–1000	1–2	B48 (A-I, Cs)
VLDL	Liver	< 1.006	40–50	10	B100 (AI, Cs)
IDL	VLDL	1.006–1.019	25–30	18	B100, E
LDL	IDL	1.019–1.063	20–25	25	B100
HDL	Tissue	1.063–1.210	6–10	40–55	A-I (A-II, A-IV)
Lipoprotein (a)	Liver	1.051–1.082	25	30–50	B100, (a)

Adapted from “Lipoprotein disorders and cardiovascular disease,” by J. Genest, P. Libby, & A. M. Gotto, 2005, in D. P. Zipes, P. Libby, R. O. Bonow, & E. Braunwald (Eds.), *Braunwald’s heart disease: A textbook of cardiovascular medicine* (pp. 1013–1033), Philadelphia: Elsevier Saunders.

- Lipids are metabolized by means of two pathways: exogenous and endogenous. Both are active processes, one for the lipids that our body produces (genetically programmed) and the other for the lipids that we ingest (lifestyle). Either one or the interaction of both can be responsible for the overall lipid status of the person.
  - Exogenous pathway
    - Chylomicrons formed from dietary TG and cholesterol
    - Lipoprotein lipase from adipose and muscle removes TG, leaving chylomicron remnants (cholesterol)
    - Remnants reach the liver where cholesterol is released and
      - Stored as esters in hepatocytes
      - Released in bile as cholesterol or bile acids
      - Used to form membranes or endogenous lipoproteins
  - Endogenous pathway
    - VLDL formed in liver from TG and cholesterol from caloric intake
    - VLDL released in plasma
    - Lipoprotein lipase cleaves TG
    - Remnant is IDL, which is taken up in liver and results in free cholesterol or remains in circulation where TG removed, leaving LDL
    - LDL transports endogenous cholesterol ester to liver
    - Apolipoprotein B is found in LDL and VLDL
    - HDL involved in transport of cholesterol from periphery to liver
  - A third pathway is nonspecific, the result of macrophage participation in lipoprotein degradation with deposits in select sites including arterial walls and tendons.
    - Clinically this can be seen as eruptive xanthomas (growths often on the elbow) or xanthelasma (deposits on the upper eyelid).
    - Aggressive treatment may be needed to arrest or remove these deposits.

## HYPERLIPIDEMIA

Hyperlipidemia is often described as having heredity or secondary cause.

- Hereditary causes are primarily the result of
  - Familial hypercholesterolemia
  - Familial hyperchylomicronemia
  - Dysbetalipoproteinemia
  - Familial combined hyperlipidemia
- Fredrickson's Classification of Genetic Hyperlipidemias is presented in Table 10–2.
- Secondary causes of hyperlipidemias include
  - Metabolic: diabetes, glycogen storage deficits, lipodystrophy
  - Renal: chronic renal failure, glomerulonephritis
  - Hepatic: obstructive liver disease, cirrhosis
  - Hormonal: estrogen, progesterone, growth hormone, hypothyroidism, corticosteroids
  - Lifestyle: obesity, physical inactivity, high-fat diet, increased alcohol intake
  - Medications: corticosteroids, exogenous estrogens, testosterone, thiazide diuretics, selective beta blockers, cyclosporine, antiretrovirals

**Table 10-2. Fredrickson's Classification of Genetic Forms of Hyperlipidemia**

Type I	Exogenous hyperlipidemia: total cholesterol normal, triglycerides and chylomicrons increased
Type IIa	LDL and total cholesterol increased
Type IIb	LDL, VLDL, total cholesterol, triglycerides increased
Type III	Dysbetalipoproteinemia: IDL, total cholesterol, and triglycerides increased
Type IV	Endogenous hyperlipidemia: glucose intolerance
Type V	Mixed hyperlipidemia

- Serum lipoprotein laboratory testing has traditionally only measured total cholesterol, HDL-C, and triglycerides. LDL is estimated based on the Friedewald Formula.
  - There is a fairly consistent ratio between VLDL and triglycerides. This is expressed as  $VLDL - C = \text{triglycerides} \div 5$ .
  - Most cholesterol is carried on three lipoproteins: HDL, LDL, and VLDL, so total cholesterol = HDL + LDL + VLDL.
  - If we measure triglyceride level, we can calculate an estimate of the VLDL.
  - If we measure total cholesterol, HDL, and TG, we can calculate an estimate for the LDL.
  - When TG is elevated (usually > 250 mg/dl), it is unwise to use this formula to estimate the LDL because there is too much error in the estimation.
  - At times it is important to know the non-LDL level and that is calculated as non-LDL-C = HDL + (triglycerides  $\div$  5).
  - The 2004 Update in the ATP III guidelines recommended that LDL-C be directly measured and not calculated; however, this has not been universally adopted. More direct measurement of LDL and subparticles is expected to be done over the next few years.
- Hypertriglyceridemia is often associated with type 2 diabetes mellitus (DM) and pancreatitis. If the patient has DM, improved blood sugar control will lower TG levels and should be done in conjunction with TG-lowering medications

## SCREENING FOR ATHEROSCLEROSIS RISK

In all adults (20 years and older), a fasting lipoprotein profile (total cholesterol, LDL-C, HDL-C, and TG) should be obtained once every 5 years. New guidelines recommend screening children between the ages of 2 and 10 years. A 12-hour fast prior to the blood draw improves the accuracy of TG. Because LDL is most often calculated based on triglyceride levels, the LDL may not be accurate if the person is not fasting. Total cholesterol and HDL measurement is not as sensitive to fasting state as triglycerides. Other atherosclerosis risk factors should also be assessed. (Assessment and management of cardiac and vascular risk is discussed in Chapters 7 and 8 of this manual.)

- Modifiable risk factors
  - Cigarette smoking
  - Uncontrolled diabetes mellitus (Hemoglobin A1C > 6%)
  - Uncontrolled hypertension
  - Obesity

- Sedentary lifestyle
- Atherosclerotic dyslipidemia
  - Low HDL cholesterol (< 40 mg/dL)
  - High LDL cholesterol (> 160 gm/dL)
  - High triglycerides (> 150 mg/dL)
- Nonmodifiable risk factors
  - Family history of early myocardial infarction (MI) or sudden death (first-degree male relative before 55 years or first-degree female relative before 65 years)
  - Increased age: men older than 45 years and women older than 55 years
  - Early onset of menopause because of total abdominal hysterectomy
- People with multiple risk factors should be screened more frequently than every 5 years, regardless of gender or race.
  - Rapid-result machines can give an entire lipid panel from a drop of blood within 5 minutes.
- Risk reduction is an important component of prevention and treatment of atherosclerosis and CHD.
- The presence of risk factors determines the acceptable level of blood lipids and the level at which pharmacological reduction should be initiated.

## ATP III GUIDELINES

The purpose of the guidelines is to provide direction to healthcare providers in the prevention and treatment of dyslipidemia in people with and without CHD.

### ATP III Classification

- For the general adult population, ATP III classification of LDL, total, and HDL cholesterol (mg/dL) is the following:
  - LDL cholesterol
    - Under 100 is optimal.
    - 100 to 129 is near but above optimal.
    - 130 to 159 is borderline high.
    - 160 to 189 is high.
    - 190 or above is very high.
  - Total cholesterol
    - Under 200 is desirable.
    - 200 to 239 is borderline high.
    - 240 or above is high.
  - HDL cholesterol
    - Under 40 is low.
    - 60 or above is high (desirable).
- Major risk factors (exclusive of LDL cholesterol) that modify LDL treatment goals
  - Cigarette smoking
  - Hypertension
  - Low HDL cholesterol
  - Family history of premature CHD
  - Age (men 45 years and older; women 55 years and older)

- LDL treatment goals related to risk
  - For people with clinical CHD or CHD risk equivalents, the LDL goal is under 100 mg/dL.
  - For people with more than two major risk factors, the LDL goal is under 130 mg/dL.
  - For people with no or one major risk factor, the LDL goal is under 160 mg/dL.

### **CHD Risk Equivalents**

- CHD risk equivalents include
  - Other forms of clinical atherosclerotic disease (i.e., peripheral arterial disease, abdominal aortic aneurysm, symptomatic carotid artery disease)
  - Diabetes
  - Multiple risk factors that confer a 10-year risk for CHD of 20% or more.
    - For people with two or more risk factors, data from the Framingham Heart Study are used to estimate the 10-year risk of CHD.
    - Points are assigned by gender for age, total cholesterol, HDL cholesterol, smoking, and blood pressure.
      - Point total predicts 10-year risk for CHD.
      - 10-year risk for CHD of 20% or more is a CHD equivalent and reason for more intensive lowering of LDL cholesterol
    - The Framingham scoring method is included in the ATP III guidelines, which can be downloaded from the Web site of the National Heart Lung and Blood Institute ([www.nhlbi.nih.gov](http://www.nhlbi.nih.gov)).

### **Therapeutic Lifestyle Changes**

- The ATP III report recommends a multifaceted approach to CHD risk reduction designated “therapeutic lifestyle changes (TLC).”
  - Reduced intake of saturated fats (less than 7% of total calories) and cholesterol (less than 200 mg per day)
  - Use of plant stanols and sterols (2 g per day) and increased soluble fiber (20 to 30 g per day)
    - Plant stanols and sterols are naturally occurring food substances that are combined with small amounts of canola oil and added to foods.
    - Currently, regular and “light” spreads fortified with plant stanols and sterols are available commercially.
  - Soluble fiber is found in oats, legumes, grains, vegetables, and fruits. Dietary intake is preferred over supplements.
  - Weight reduction
  - Increased physical exercise

## IMPLICATIONS FOR NURSING PRACTICE

- Nurses screen, monitor, and teach individuals and groups about the management of dyslipidemia and atherosclerotic risk.
  - Screening occurs in community and acute care settings.
    - Patients admitted to the hospital with a cardiovascular event should be screened within 24 hours of admission.
  - Individual risk assessment and modification is essential.
  - Routine monitoring of the lipid profile allows the person to observe improvement and reinforces behavior change.
    - Providing laboratory results, together with target goals, in writing enables the patient to monitor his or her progress over time.
- Nurses and dietitians are responsible for teaching people about therapeutic lifestyle changes.
- Nurses monitor the therapeutic and side effects of pharmacotherapy and promote patient adherence.

## TREATMENT OF DYSLIPIDEMIA

### Primary Prevention

- Primary prevention consists of screening and therapeutic lifestyle changes (TLC).
- TLC dietary recommendations include
  - Total fat (saturated, polyunsaturated, and monounsaturated) should not exceed 25% to 30% of total calories.
    - Saturated fat should constitute less than 7% of total calories.
    - Polyunsaturated fats may be up to 10% of total calories.
    - Monounsaturated fats may be up to 20% of total calories.
  - Carbohydrates (primarily whole grains, fruits, and vegetables) may be up to 50% to 60% of total calories.
  - Fiber should be 20 to 30 grams per day.
  - Protein should constitute approximately 15% of total calories.
  - Cholesterol should be less than 200 mg per day.
  - Total calories consumed should be balanced with energy expended to achieve and maintain desirable body weight.
    - When TG is elevated, advise the patient to decrease sugar and alcohol intake.
- If the target lipid levels are not achieved after 6 weeks with the TLC diet, plant stanols and sterols are added.
- If target lipid levels are not achieved after 12 weeks, pharmacotherapy is initiated. LDL-lowering drugs reduce the risk for major coronary events and coronary death.
- At each visit, TLCs are reviewed and reinforced, even after drug treatment is begun.
- Pharmacologic therapy should be started if patient is unresponsive to TLC; if the patient is at high risk, medications are started along with TLC.
- The primary target is to treat LDL-C to goal.
- The secondary targets are to raise HDL-C and lower TG if not at goal.
  - Exercise can raise HDL-C.
  - Reducing intake of simple carbohydrates and alcohol can lower TG.

## Secondary Prevention

- Cholesterol treatment goals for people with clinical CHD or CHD equivalents are more stringent.
  - LDL cholesterol should be less than 100 mg/dL or, in the very high risk group, less than 70 mg/dL.
- Lipid profile should be obtained within 24 hours of hospital admission for an acute coronary event and therapy should be initiated before discharge.
  - Current guidelines recommend starting HMG-CoA reductase inhibitors (statins) on all patients after CHD is diagnosed.
  - ATP III guidelines recommend starting a fibric acid derivative or nicotinic acid, if appropriate for secondary target therapy.
- Lipid profile should be reevaluated 6 and 12 weeks after initiating drug treatment.
- Therapeutic lifestyle changes and reduction of other risk factor reduction should be encouraged also.

## Drug Therapy

- Drugs used to treat dyslipidemia are described in detail in Chapter 15.
- HMG-CoA reductase inhibitors, also known as statins, decrease mortality, reduce the risk of major coronary events by 30%, and stimulate plaque regression in coronary heart disease.
  - Statins are most effective when taken at bedtime.
  - Statins decrease LDL (18% to 55%), increase HDL (5% to 15%), and decrease triglycerides (7% to 30%).
  - Statins can be combined with nicotinic or fibric acids if necessary.
  - Statins are contraindicated in people with active or chronic liver disease.
  - Liver enzymes are assessed after 6 weeks and every 6 months during treatment. Discontinue the statin if liver function tests (LFTs) are more than three times the upper limit of normal (ULN).
  - Statins also can reduce the inflammatory marker high-sensitivity C-reactive protein (hs-CRP) and are thought to reduce inflammation at the site of an atherosclerotic lesion, resulting in a more stable lesion that is less likely to rupture and cause an MI.
  - Patients must be taught to report symptoms of muscle aches or weakness.
    - Myalgia with normal creatine kinase (CK) may occur in up to 5% of those on a statin.
    - Myopathy is muscle aches with CK more than 10 times ULN, which occurs in less than 0.1%.
    - Rhabdomyolysis—breakdown of the muscle cells with CK above 10,000 IU/L—is rare (< 0.01%).
    - The highest risk for rhabdomyolysis is in elderly, women, small frame, dehydrated, hypothermia, acidosis, chronic disease, infection, alcohol abuse, extreme exercise, and cytochrome P450 interactions.
- Bile acid sequestrants
  - Decrease LDL (15% to 30%) and increase HDL (3% to 5%) without affecting triglycerides.
  - May be added to statin therapy in people who do not reach target levels on statins alone.
  - Side effects include gastrointestinal (GI) distress and constipation.
  - May interfere with absorption of other drugs.

- Nicotinic acid
  - Decrease LDL (5% to 25%) and triglyceride (20% to 50%) and increase HDL (15% to 35%).
  - Side effects include flushing, hyperglycemia, hyperuricemia (gout), upper GI distress, and hepatotoxicity.
- Fibrates (gemfibrozil, fenofibrate, clofibrate)
  - Decrease LDL (5% to 20%) and triglyceride (20% to 50%) and increase HDL (10% to 20%).
  - Side effects include dyspepsia, gallstone, and myopathy. Unexplained non-CHD deaths were seen in clinical trials.
  - Contraindicated in severe renal or hepatic disease.
- Cholesterol absorption inhibitors (ezetimibe)
  - Work on the brushy border of the small intestine, inhibiting the absorption of cholesterol and other sterols.
  - This drug can achieve 18% LDL-C–lowering alone and can be used if a statin is not tolerated.
  - It can also be added to a statin to achieve lower LDL-C if on maximal statin dose.
- Omega-3 polyunsaturated fatty acids (PUFA) are found in the diet in oily fish or can be provided as supplements.
  - Increase HDL-C and can be used with statins and other pharmacotherapies.
  - Similar PUFAs are found in nuts (e.g., walnuts, almonds).

## METABOLIC SYNDROME

Metabolic syndrome is present in approximately 22% of the adult (20 years and older) population. People with the metabolic syndrome have an increased risk of developing atherosclerosis and a higher incidence of cardiac events than those without this syndrome. Metabolic syndrome is a growing problem in children and adolescents.

- The metabolic syndrome consists of lipid and nonlipid factors. The presence of any three of the five factors makes the diagnosis of metabolic syndrome. The factors are
  - Triglyceride 150 mg/dL or higher
  - HDL cholesterol below 40 mg/dL in men and below 50 mg/dL in women
  - Abdominal obesity (waist circumference over 40 inches in men and over 35 inches in women)
  - Elevated BP (130/85 mm Hg or higher)
  - Glucose intolerance (fasting blood glucose above 110 mg/dL).
- Treatment of metabolic syndrome is a secondary target in managing dyslipidemia. That is, after LDL cholesterol is reduced, further risk reduction can be achieved by treating the metabolic syndrome.
- Likewise, weight reduction and hyperglycemia and hypertension treatment should be aggressive to reduce the risk of CHD.

**Table 10–3. Treatment Recommendations Based on Direct Measurement of Lipid Subclasses**

Elevated LDL	Statin
Elevated Lp(a)	Niacin
Elevated IDL	Statin + niacin, fibrate
Pattern B, A/B	Omega-3 fatty acids, niacin, fibrate, statin
Low HDL2	Omega-3 fatty acids, niacin, fibrate
VLDL, Triglycerides	Omega-3 fatty acids, niacin, fibrate, some statins

## NEW APPROACHES TO LIPID ASSESSMENT

- While several different methods exist, subparticles in lipoproteins are generally determined through electrophoresis, which separates the serum cholesterol based on the size of particles.
- LDL is most often calculated and not directly measured. When calculated it predicts 40% of the variance in CHD. However, when LDL is measured directly the prediction increases to 90%.
  - LDL, HDL, VLDL, triglycerides, non-HDL (LDL + VLDL) have same range as traditional tests.
  - Subclass measurement of HDL (2a, 2b, 3a, 3b, and 3c) and LDL (I, IIa, IIb, IIIa, IIIb, IVa, IVb) are measured along with lipoprotein (a), IDL, and VLDL.
    - Smaller LDL particles are more atherogenic than larger LDL particles.
    - HDL-2 is larger and most protective while HDL-3 is smaller, denser, and least protective.
  - Pattern A, which is desirable, can be determined.
  - Pattern B, which has the highest risk for atherosclerosis and metabolic syndrome, is identified.
- Therapies can be more appropriately prescribed based on subclasses. Table 10–3 provides the overview of treatment based on knowledge of subclasses.

## SUMMARY

This chapter provided an overview of lipids, lipid metabolism, and risk in cardiovascular disease. Current treatment goals and therapies are part of the ATP III guidelines. The fourth edition will be published in the near future so be sure to stay updated on this information. More data on the use of subclasses of lipid components will continue to drive risk reduction efforts.

## REFERENCES

- Berra, K. (2008). Lipid lowering therapy today: Treating the high-risk cardiovascular patient. *Journal of Cardiovascular Nursing*, 23(5), 414–421.
- Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. (2001). Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA*, 285, 2486–2497.
- Genest, J., Libby, P., & Gotto, A. M. (2005). Lipoprotein disorders and cardiovascular disease. In D. P. Zipes, P. Libby, R. O. Bonow, & E. Braunwald (Eds.), *Braunwald's heart disease: A textbook of cardiovascular medicine* (pp. 1013–1033). Philadelphia: Elsevier-Saunders.
- Gissi-HF Investigators, Tavazzi, L., Maggioni, A. P., Marchioli, R., Barlera, S., Franzosi, M. G., ... Tognoni, G. (2008). Effect of n-3 polyunsaturated fatty acids in patients with chronic heart failure (the GISSI-HF trial): A randomised, double-blind, placebo-controlled trial. *Lancet*, 372(9645), 1223–1230.
- Grundy, S. M., Cleeman, J. I., Merz, C. N., Brewer, H. B. Jr., Clark, L. T., Hunninghake, D. B., ... American Heart Association. (2004). Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. *Circulation*, 110, 227–239.
- Hughes, S. (2007). Dyslipidemia. In D. Moser & B. Reigel (Eds.), *Cardiac nursing: A companion to Braunwald's heart disease* (pp. 418–430). St. Louis, MO: Elsevier-Saunders.
- Jarvis, C. M., Hayman, L. L., Braun, L. T., Schwertz, D. W., Ferrans, C. E., Piano, M. R. (2007). Cardiovascular risk factors and metabolic syndrome in alcohol and nicotine dependent men and women. *Journal of Cardiovascular Nursing* 22(3), 429–435.
- Ridker, P. M., Danielson, E., Fonseca, F. A., Genest, J., Gotto, A. M. Jr, Kastelein, J. J., ... JUPITER Study Group. (2008). Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *New England Journal of Medicine*, 359, 2195–2207.
- Pagana, K. D. (2007). What's the latest on lipoproteins? *American Nurse Today*, 2(11), 41–42.