Indian Journal of Medical & Health Sciences
Volume 3 Number 2, July - December 2016
DOI: https://dx.doi.org/10.21088/ijmhs.2347.9981.3216.9

Review Article

Evaluation and Interpretation of Lipid Profile Based on the National Cholesterol Education Programme Adult Treatment Panel III Guidelines

Mallick Ayaz K.*, Marya Ahsan**

IJMHS (Jul-Dec 2016) 03 (02): 129-135 / ©Red Flower Publication Pvt. Ltd.

Abstract

Disorders of lipids and their transporting molecule, i.e. the lipoproteins, are well known to cause cardiovascular diseases (CVD) and death. Evaluation of lipid status of an individual mainly consist of determination of Total Cholesterol (TC), Triglyceride (TG), Low density lipoprotein-cholesterol (LDL-C) and High density lipoprotein-cholesterol (HDL-C) levels in their plasma or the serum. For over three decades lots of emphasis has been given to these molecules. Various guidelines were laid down for the evaluation of these parameters which were then modified regularly in order to improve the quality of life. The National Cholesterol Education Program–Adult Treatment Panel (NCEP-ATP) released its first guidelines in 1988. Continuous updates and modification has been done till date. Recently many new and novel analytes have shown strong correlation with CVD. Some of these analytes includes Apo A1, Apo B100, Lipoprotein(a) [Lp(a)], Lipid Associated Phospholipase A2 (LpA2), LDL particle number, homocysteine and high sensitive C Reactive Protein (hs-CRP). This review article is written with the intention to highlight the diagnostic guidelines, grouping of individuals based on risk factors, therapeutic targets and approach towards management of dyslipidemia based on the criteria put down by NCEP-ATP III. Above mentioned novel markers are also highlighted as they hold lots of potential in improving the quality of health care provided to risk population.

Keywords: Lipid; Lipoproteins; Extended Lipid Profile; NCEP-ATP III.

Key Message

Commonly performed test to identify dyslipidemia includes TC, TG, LDL-C and HDL-C. Within last few years many new and novels markers have been identified which shows strong correlation with CVD. These markers may soon be included in routine evaluation of dyslipidemia.

Introduction

Lipids are ubiquitous macromolecules present in almost all the body tissues. It performs many vital functions such as source of energy, functional and structural component of cell membranes, faster nerve conduction. They also form important component of steroid hormones. Bile salts which are synthesized from cholesterol plays important role in digestion and absorption [1].

For many years now lots of emphasis and attention has been focused on lipids and their transport vehicle, the lipoproteins, due to a strong association between dyslipidemia and development of cardiovascular diseases (CVD)which is one of the leading causes of death worldwide [2].

In 1980s, the Coronary Primary Prevention Trail (CPPT) showed that reduction in cholesterol led to decreased incidence of CAD. Along with this, many other studies showed the effect of diet, exercise, medication, reduction in weight in decreasing the incidence of CAD [3].

Author's Affiliation: *Associate Professor Department of Biochemistry, **Assistant Professor, Department of Pharmacology, Rohilkhand Medical College, Bareilly.

Reprint Request: Ayaz Khurram Mallick, Associate Professor, Department of Biochemistry, Rohilkhand Medical College and Hospital, Pilibhit Bye Pass Road, Bareilly (U.P.) 243006
E-mail: ayazmallick@yahoo.com

Based on the data available from all these studies, the National Heart, Lung and Blood Institute (NHLB) established the National Cholesterol Education Program (NCEP) which dealt with increasing public awareness and design strategies for diagnosis and treatment of dyslipidemia. This was then called as NCEP-ATP (Adult Treatment Panel). First guidelines were released in 1988. This was then followed by ATP-II in 1993. In 2001, NCEP-ATP III guidelines were released which was implemented in 2004 [3].

Lipoproteins

As lipids are insoluble in aqueos medium, they are transported in the blood by forming complexes with proteins. These complexes are called as lipoproteins. They are spherical in shape consisting of an inner core, which comprises of triacylglycerol (TAG) and cholesteryl esters (CE), and an outer layer comprising of phospholipids (PL) and free cholesterol. The inner core in hydrophobic where as the outer layer is hydrophilic due to presence of proteins. Based on the composition i.e. type of cholesterol and proteins, these lipoproteins varies in their density and are classified accordingly [4].

Basic Lipid Profile

Lipid profile means determination of various lipids or lipoproteins in the blood in order to obtain information regarding them. Basic lipid profile involves determination of serum triglyceride (TG), serum total cholesterol (TC), high density lipoprotein cholesterol (HDL-C) and low density lipoprotein cholesterol (LDL-C).

Collection of Blood Sample

Traditionally a fasting venous sample of 9 to 12 hours is collected. Prior to collection of blood sample, the patients is advised to take proper diet for three consecutive days.

During this period the patient should not eat anything. Drinking plain water may be permitted [5]. However, if fasting sample cannot be collected, non-fasting sample may be collected. The Canadian Cardiovascular Society, in their 2012 Dyslipidemia Guidelines, introduced the use of non-fasting specimens for lipid assessment with theintroduction of non-HDL-C and apo-B as alternate lipid assessment targets. Neither non-HDL-C nor Apo Bare affected by the patient's fasting status. If the serum triglyceride levels are more than 180 mg/dL in a non fasting sample then, it is advisable to determine the lipid profile with a fasting sample [6]. The reference range of components of lipid profile is summarized in Table 1.

Table 1: Reference values of lipid profile based on NCEP-ATP III guidelines [8]

Total Cholesterol	
Below 200 mg/dL	Desirable
200 - 240 mg/dL	Borderline high
Above 250 mg/dL	High
LDL Cholesterol	
Below 100 mg/dL	Optimal
100 – 129mg/dL	Above optimal
130 – 159 mg/dL	Borderline high
160 – 189 mg/dL	High
Above 190 mg/dL	Very high
HDL Cholesterol	
40 mg/dL and below	Low
60mg/dL and above	High
Triglycerides	
Below 150mg/dL	Normal
150 – 199 mg/dL	Borderline high
200 – 499 mg/dL	High
500 mg/dL and above	Very high

Indication to Assess Lipid Profile [6]

Patients of any age group may be assessed if the physician requires.

Patients with high risk factors

- Males over 40 years of age.
- Post menopausal women or females over 50 years of age.
- Patients with history of coronay artery disease, peripheral arterial disease (PAD), aortic aneurysm, carotid artery disease

- Patients with diabetes mellitus
- Hypertensive patients (BP > 140/90 mmHg)
- Cigarette smoking
- Family history of premature CAD
- Abdominal obesity: men with waist circumference above 40 inches and females with waist circumference above 35 inches

Classification of patients based on risk factors

The guideline for classifying patients into different groups is proposed by NCEP-ATP III. Basis of this grouping is [3,7]:

a. Presence of number of risk factors
b. 10 year Framingham risk scaling

Framingham risk scaling is based on point scoring system which takes into consideration the age, total cholesterol levels, smoking, blood pressure. If the 10 year risk assessment is greater than 20%, it is considered as CHD risk equivalent.

- Low risk: A patient with no risk or just one risk factor.
- Moderate risk: A patient with two or more risk factor and 10 year Framingham scaling between 10 – 20%.
- High risk: Patients with existing CAD, CHD equivalents (Diabetes mellitus, abdominal aortic aneurysm) and a 10 year Framingham scaling above 20%.
- Very high risk group: Patients with recent myocardial infarction, metabolic syndrome or continuous smoking.

Low Density Lipoprotein Cholesterol

LDL-C are involved in transportation of cholesterol from the liver to the extra hepatic tissue such as arteries and other tissues. According to the NCEP-ATP III, reduction in the LDL-C is the primary target in treatment of dyslipidemia [8].

As LDL-C undergoes oxidative damage, it can activate the scavenger receptor Class A pathway in the macrophages leading to formation of foam cells and hence atherosclerosis [1]. In view of this, the major approach of NCEP-ATP III is based on reduction of LDL-C levels.

High Density Lipoprotein Cholesterol

HDL-C plays a very important role in reverse cholesterol transport. They are synthesized in the liver and intestine. Initially they are discoid shaped and as they circulate in the blood, they remove cholesterol from cholesterol laden cells and returns it to the liver.

In spite of the ability of HDL-C to remove the cholesterol from circulation, NCEP does not include HDL-C as an important parameter for targeting or monitoring therapy [8].

Triglycerides

Triglycerides are the storage form of fatty acids. They are synthesized mainly in the liver and the intestine and stored in the adipose tissue. As the triglyceride levels are affected by the diet, fasting blood samples are compulsory. As most of the triglycerides are present in the VLDL-C it is considered as a surrogate marker of VLDL-C. VLDL-C is calculated from triglycerides by using the Friedwald's formula.

Non HDL Cholesterol

This includes all the lipoproteins which contains Apo B as their apoprotein. This is derived by subtracting HDL-C from TC. As per the guidelines by the NCEP-ATP III, determination of non HDL-C is the secondary target for patient with dyslipidemia particularly high triglycerides levels. If the levels of triglycerides exceeds 400 mg/dL, the levels of LDL-C may not be reliable. Therefore is such cases, the non HDL-C is considered for therapeutic goal. The target levels for non HDL-C is concentration LDL-C plus 30.

Recently, the American Diabetes Association and the American College of Cardiology Foundation have proposed to use non HDL-C as a marker for cardiovascular risk factor in patients with low to moderate LDL-C levels. Advantages of using non HDL-C over LDL-C is that, it is easily calculated, non-fasting samples can be used and is less expensive [6,12]. Current literature suggests that non-HDL-C and Apo–B are more reliable indicators of CVD than LDL-C [11,12].

Approach to Dyslipidemia

Management of a patient with dyslipidemia is done at two levels:

a) Therapeutic lifestyle changes (TLC) mainly based on lifestyle modification
b) Drug therapy

The choice of therapy depends upon the levels of LDL-C.

Therapeutic Targets [7,8]

The management of dyslipidemia consists of primary and secondary goal targets. These targets are based on the LDL-C and non HDL-C levels. This is summarized in Table 2.

Indication of Therapy [7,8]

Table 2: Table showing the primary and the secondary therapeutic target as per the ATP III guidelines

Risk category	Primary target (LDL Goal)	Secondary target (Non HDL Goal)
High risk	< 100 mg/dL	< 130 mg/dL
Moderate risk	<130 mg/dL	< 160 mg/dL
Low risk	< 160 mg/dL	< 190 mg/dL

Table 3: Table showing the therapeutic indication in different risk group as per the ATP III guidelines.

Risk category	LDL goal	TLC	Drug therapy
High risk	< 100 mg/dL	≥ 100 mg/dL	≥ 130 mg/dL
Moderate risk	< 130 mg/dL	≥ 130 mg/dL	≥ 130 mg/dL
			≥ 160 mg/dL
Low risk	< 160 mg/dL	≥ 160 mg/dL	≥ 190 mg/dL

Therapy is indicated if the LDL-C exceeds the goal targets. Summary of therapeutic indication is given in Table 3.

Therapeutic lifestyle Changes

TLC is concerned with lifestyle modification. Components of TLC includes [5]:

- TLC diet: Patient should avoid high fat diet. Total lipid intake should be restricted to less than 30% of caloric requirement. Saturated fat intake must not exceed more than 7% of caloric requirement. Intake of mono unsaturated and poly unsaturated fatty acids should be increased. Cholesterol intake should be limited to less than 200 mg/day. Patient should increase the consumption of dietary fibres and plant sterols. Fruits should be taken every two to three hours. Plant sterols are structurally similar to cholesterol therefore competes for absorption.
- Weight management: Overweight and obesity particularly abdominal obesity makes a person more prone for metabolic syndrome. The weight size is a better indicator to judge overweight than body mass index (BMI).
- Increased physical activity

Drug Therapy

Drug therapy is indicated immediately in high risk group patients. In case of moderate and low risk group patient drug therapy is started if the LDL-C or primary goal is not achieved by TLC within 3 months. Commonly prescribed drugs are summarized below [13].

- *HMG CoA Reductase Inhibitors:* These group of drugs are structurally similar to HMG CoA reductase which is the key regulatory enzyme in cholesterol synthesis. Hence they competitively inhibit the enzyme. Their main action comprises reduction in TC and LDL-C levels. Major side effects includes myopathy and elevated liver enzymes. Hence they are contraindicated in liver disorder.
- *Fibric Acid:* These drugs activates the Peroxisome Proliferator Activated Receptor alpha (PRPP-α). Once activated, they then activate the lipoprotein lipase resulting in reduction in triglyceride levels. This PRPP-α also increases the Apo A-1 which increases the HDL-C. Side effects includes dyspepsia, myalgia, myositis. These drugs are contraindicated in patients with cholethiasis and liver disorder.
- *Bile Sequestrants:* These drugs, as their name suggests, binds to the bile salts in the intestine and prevents the enterohepatic circulation reduces the absorption of cholesterol. This increases the hepatic cholesterol synthesis leading to increase uptake of LDL-C. There is also a paradoxal increase triglyceride. Side effects include constipation.
- *Nicotinic Acid:* These drugs reduces the VLDL-C and LDL-C levels and also increases the HDL-C levels. Major side effects includes hyperuricemia, impaired glucose tolerance and hepatic toxicity.

Monitoring of Treatment

Once dyslipidemia has been identified and patients are categorized based on the risk group, the treatment is started. Fasting lipid profile is assessed frequently. Patients who are on TLC, fasting lipid profile is done every three to six months for a period of one year. Thereafter, the fasting lipid profile is assessed every six to twelve months. In those patients who require drug therapy, the fasting lipid profile is determined every two to three months in the first year. After that lipid profile is assessed every six to twelve months. Liver function, renal function and creatine kinase are also determined simultaneously as the drugs can cause side effects [8].

Extended Lipid Profile / Advanced Lipid Profile

Apart from the basic lipid profile which measures the triglyceride, total cholesterol, LDL-C and HDL-C, many other tests are also being performed. These include ApolipoproteinA 1, Apolipoprotein B 100, highly sensitive C- reactive protein (hs CRP), homocysteine, lipoprotein (a), lipoprotein associated phospholipase A_2. Some of these molecules like apolipoproteins, Lp (a) are lipids in true sense whereas the other are included here because of their close association with lipids.

Apolipoprotein A 1

Apo A1 is the major protein component of HDL-C. It participates in the reverse cholesterol transport by forming pre â 1 HDL which takes up the free cholesterol. Concentration of Apo A1 in normal individual is around 100 – 200 mg/dL. Levels are decreased in smokers, uncontrolled diabetes mellitus, chronic renal failure. Inspite of its close association with HDL-C, it is not recommended by NCEP ATP III. However it is helpful in patients with family history of coronary heart disease and when genetic cause of dyslipidemia is suspected [14].

Apolipoprotein B 100

Apo B 100 is the major protein found in VLDL-C and LDL-C. Various studies have suggested that Apo B 100 is a better marker of coronary artery disease (CAD) in comparison LDL-C and non HDL-C. Normal levels of apo B 100 is 55 – 140mg/dL. As Apo B 100 has shown a strong positive predictive power for severity of CAD it is accepted as an alternative test by ATP III. Consensus by ADA and ACCF recommends Apo B100 to be a very sensitive marker [14].

High Sensitive C reactive Protein (hs-CRP)

Hs CRP is an acute phase protein released during inflammation, therefore it is a marker of systemic inflammation. It is an independent risk factor for CHD, stroke and peripheral vascular disease. If done along with lipid profile it adds up to its predictive value. It is estimated in patient with 10 year Framingham Risk Scale between 10 – 20% [15].

Homocysteine

Homocysteine is a thiol containing amino acid derived from methionine. Causes of increased homocysteine levels are genetic defect, deficiency of vit B6, vit B12 or folic acid and renal disorders. Most common genetic defect includes a thrombolabile variant of methylene tetrahydrofolatereductase (MTHFR). Hyperhomocysteinemia is an independent risk factor for development of coronary or cerebral vascular disease. Currently, NCEP ATP III does not recommend homocysteine for evaluation of dyslipidemia. However it may be useful in presence of family history of premature CHD [16].

Lipoprotein (a)

Lp(a) are cholesterol rich lipoprotein particles which are structurally and compositionally similar to LDL-C. Patients who have Lp(a) levels greater than 50mg/dL have two to three times more risk of developing CAD. Lp(a) estimation is recommended by NCEP ATP III especially for those individuals with strong family history of premature CHD [17].

Lipoprotein Associated Phospholipase A2

Lp A2 is also called as platelet activating factor acetylhydrolase (PAF AH). They are produced by inflammatory cells particularly the vascular endothelial cells. They are bound to LDL-C and therefore hydrolyses the pphospholipids on the LDL-C to produce oxidized free fatty acids and lysophosphatidylcholine. Both these product are highly atherogenic. Lp A2 is considered as a risk marker for CAD. Levels greater than 235 mg/dL is associated with MI and stroke. Increase Lp A2 along with low LDL-C increases the risk of CAD by 2 times. However, increase Lp A2 along with high hs CRP increases the risk of heart disease by 3 times [18].

LDL Particle Number

LDL particle number is an emerging area of interest. As the LDL-C is being circulated it varies in size. The

size may be small, large or intermediate. Small LDL are more atherogenic than large LDL. Smaller the size greater is the density of LDL-C. LDL number can be measured by Nuclear Magnetic Resonance (NMR), ultracentrifugation and HPLC [19].

Although it has high predictability, it is not used routinely as it is very expensive and there is not enough data in regards to population and age.

Vertical Auto Profile (VAP)

The VAP test was developed in 2006. According to this, 15 different tests can be reported instead of the current four. It utilizes the vertical density gradient ultracentrifugation method. This test can measure the LDL-C directly. It meets the criteria of ADA and ACCF as it can measure LDL-C, non HDL-C and Apo B. Apart from these it can estimate the number of LDL, type of HDL, estimate Lp(a) and other proteins.

Potential Changes for ATP IV

Since the implementation of ATP III in 2004, many new parameters have been identified. ATP IV is keenly anticipated. It was expected to be released in 2012 but was delayed. Some of the potential changes that may be done in ATP IV are as follows [20].

1. Addition of chronic kidney disease as CHD equivalent
2. With regards to changes in the therapeutic goal
   a. Therapeutic target for LDL-C may be reduced to < 70 mg/dL instead of the current < 100 mg/dL for high risk group. Infact many trials and studies have already reduced the target to < 70 mg/dL.
   b. Addition of Apo B as a therapeutic goal
   c. Addition of hs CRP
3. Framingham Risk Assessment tool may be replaced withReynold's Risk Assessment tool.

Summary

Lipids are essential macromolecules performing various vital function for normal wellbeing of an individuals. However, any metabolic alteration either in their synthesis, metabolism or breakdown can lead to various disorders which are associated with coronary heart disease. In order to prevent and appropriately manage dyslipidemia, the NCEP ATP III laid down the guidelines for evaluation, approach and therapeutic goals. Patients are divided into risk groups based on the risk factors and Framingham risk assessment tool. The NCEP ATP III identifies LDL-C as primary target for management and non HDL-C as the secondary target. There are two modalities of management beginning initially from Therapeutic Life Style Changes and then extending to drug therapy if required. Recently various new parameters like Apolipoproteins, CRP, Lp-PLA2, Lp(a) have proved significant is assessing a patient with lipid disorder. Inclusion of some of these new parameters by ATP IV is keenly awaited which would add new dimension to evaluate a patient with dyslipidemia.

References

1. Harvey RA, Ferrier DR. Lippincott's Illustrated Reviews: Biochemistry (Lippincott s Illustrated Reviews Series). 6th ed. Philadelphia: Lippincott Williams and Wilkins; 2013.
2. Roger VL, Go AS, Loyd-Jones DM, et al. Heart disease and stroke statistics – 2012 update: A report from the American Heart Association. Circulation. 2012; 125(1): e2-e220.
3. Grundy SM, Cleeman JI, Merz CNB, Brewer HB, Clark LT, Hunninghake DB, Pasternak RC, Smith SC, Stone NJ. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. Circulation. 2004 Jul 13; 110(2): 227–39.
4. Murray RK, Bender D, Botham KM. Harper's Illustrated Biochemistry. 29th ed. New York: McGraw-Hill Medical; 2012 Apr 1. ISBN: 9780071765763.
5. Vasudevan DM, Sreekumari S, Vaidyanathan K. Textbook of Biochemistry for Medical Students. 7th ed. India: Jaypee Brothers Medical Publishers; 2013 Aug 31. ISBN: 9789350905302.
6. Guidelines for lipid testing. Community laboratories guidelines. Ontorio Association of Medical Laboratories. http://hin.nhlbi.nih.gov/atpiii/riskcalc.htm
7. ATP III Guidelines At-A-Glance Quick Desk Reference. National Cholesterol Education Program. NIH Publication No. 01-3305. May 2001.
8. 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). Final report. National Cholesterol Education Program. NIH 2012.
9. Greenland P, Alpert JS, Beller GA, et al. 2010 ACCF/ AHA guideline for assessment of cardiovascular risk in asymptomatic adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am CollCardiol. 2010; 56: e50-e103.
10. Ramjee V, Sperling LS, Jacobson TA. Non–High-

Density Lipoprotein Cholesterol Versus Apolipoprotein B in Cardiovascular Risk Stratification. JACC. 2011; 58 (5): 457-63.

11. Sniderman AD, Williams K, Contois JH, Monroe HN, McQueen MJ, de Graaf J et al. A meta-analysisof low density lipoprotein cholesterol, non-high-density lipoprotein cholesterol, andapolipoprotein B as markers of cardiovascular risk. CircCardiovascQual Outcomes. 2011; 4: 337-45.
12. Boekholdt SM, Arsenault BJ, Mora S, Pedersen TR, Nestel PJ, Simes RJ, et al. Association of LDLcholesterol, non-HDL cholesterol, and apolipoprotein B levels with risk of cardiovascular eventsamong patients treated with statins: a meta-analysis. JAMA. 2012; 307: 1302-9.
13. Katzung BG, Masters SB, Trevor AJ. Basic and clinical pharmacology 12/E. 12th ed. New York: McGraw-Hill Medical; 2012 Jan 1. ISBN: 9780071764018.
14. Brunzell, JD et al. Lipoprotein management in patients with cardiometabolic risk: consensus statement from the American Diabetes Association and the American College of Cardiology Foundation. Diabetes Care. 2008 Apr; 31(4): 811-22.
15. Ridker P, et al: C-reactive protein, the metabolic syndrome, and risk of incident cardiovascular events: an 8-year follow-up of 14,719 initially healthy American women. Circulation. 2005; 107(3): 391-7.
16. Armitage JM, Bowman L, Clarke RJ, et al; Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) Collaborative Group. Effects of homocysteine-lowering with folic acid plus vitamin B12 vs placebo on mortality and major morbidity in myocardial infarction survivors: a randomized trial. JAMA. 2010; 303: 2486–9.
17. Kamstrup PR, Tybjaerg-Hansen A, Steffensen R, et al. Genetically elevated Lipoprotein (a) and increased risk of myocardial infarction. JAMA. 2009; 301: 2331-2339.
18. The Lp-PLA2 Studies Collaboration: Lipoprotein-associated phospholipase A2 and risk of coronary disease, stroke, and mortality: collaborative analysis of 32 prospective studies. Lancet. 2010; 375: 1536–44.
19. Maki KC, Dicklin MR, Davidson MH, Mize PD, Kulkarni KR. Indicators of the Atherogenic Lipoprotein Phenotype Measured with Density Gradient Ultracentrifugation Predict Changes in Carotid Intima-Media Thickness in Men and Women. 2012; 8: 31–38.
20. Atherotech Website, http://www.thevaptest.com Accessed March 2012.
21. Cook NR, Paynter NP, Eaton CB, Manson JE, Martin LW, Robinson JG et al. Comparison of the Framingham and Reynolds Risk Scoresfor Global Cardiovascular Risk Prediction in theMultiethnic Women's Health Initiative. Circulation. 2012; 125: 1748-1756.