UNIT NO. 3

# SCREENING AND CLASSIFICATION OF HYPERLIPIDEMIA

Dr Loh Keh Chuan, Dr Melvin Leow Khee Shing

## PREVIEW

This unit covers the principles and pitfalls in hyperlipidemia screening, interpretation of blood test results, cutoffs values for dyslipidemia, Fredrickson phenotyping and primary and secondary hyperlipidemia.

## OBJECTIVES

At the end of this unit, the course participants should be able to describe the following:

- Principles and pitfalls in hyperlipidemia screening
- Interpretation of blood test results
- Cutpoints for dyslipidemia
- Fredrickson phenotyping
- Primary and secondary hyperlipidemia

## PRINCIPLES AND PITFALLS IN HYPERLIPIDEMIA SCREENING

Clinical recommendations and guidelines for the evaluation of hyperlipidemia have been developed by local and international experts such as the US National Cholesterol Education Program (NCEP). In developed countries such as in Europe and the United States, physicians are recommended to screen plasma lipids at least once every five years for all adults aged 20 and above. Based on the National Health Survey 1998 statistics indicating a steep increase in the incidence of hypercholesterolemia after age 40 (33.4%) compared to younger individuals (8.9% between age 18–29 and 22.7% between age 30–39), our local recommendation is to screen all individuals aged 40 years and above for plasma lipids. However, all patients with diabetes mellitus, impaired glucose tolerance, pre-existing coronary artery disease (CAD), stroke or peripheral vascular disease should be screened irrespective of their age. Earlier screening from age 30 or younger should be considered for those with risk factors for CAD or with a strong family history of primary hyperlipidemia.

For healthy individuals, random, non-fasting plasma lipids may be performed. If the total cholesterol is elevated and the HDL-C is low, it is necessary to reassess with a fasting plasma lipids. For patients with adverse coronary risks profile (eg. hypertension, family history of sudden cardiac deaths, early cardiovascular disease or multiple risk factors), established atherosclerotic disease or diabetes mellitus, the initial lipid assessment should be a full fasting lipoprotein analysis.

LOH KEH CHUAN, Senior Consultant, Endocrine Unit, Tan Tock Seng Hospital

MELVIN LEOW KHEE SHING, Associate Consultant Endocrine Unit, Tan Tock Seng Hospital

In the examination, look specifically for evidence of xanthelesma, corneal arcus, thickened tendons and xanthomata, in addition to evaluating for arterial disease (eg. palpation of peripheral pulses, auscultation for bruits over the carotid, abdominal aorta, renal and femoral arteries), target organ damage and any underlying secondary factors. Clinical evaluation should also include an assessment of weight, height, body mass index, waist circumference and blood pressure.

The potential pitfalls in screening should be known to every physician. Firstly, it is important that fasting should be over a duration of at least between 10 to 12 hours. This is particularly important for accurate estimation of TG. This differs from serum total cholesterol and HDL-C, which can be measured at any time in the non-fasting state. Also, fasting plasma lipids performed in the early phase of an acute illness such as acute myocardial infarction may be falsely depressed between 24 hours to 3 months post-infarction due to inhibition of cholesterol synthesis. In this instance, it is more accurate to assess the fasting lipids again after the patient has recovered from the acute event. Screening should be deferred for at least 2 weeks after a febrile illness. Plasma lipids should be retested at regular intervals depending on the overall CAD risks.

## INTERPRETATION OF PLASMA LIPIDS RESULTS

In general, the cutpoints for dyslipidemia are to be interpreted flexibly in the context of total risk for both adults and children. According to the Adult Treatment Panel III (ATP III) guidelines, it is recommended to establish LDL-C elevations on at least two separate fasting determinations prior to any intervention. Classification and diagnosis of dyslipidemia depend on the cutpoints of total cholesterol (TC), LDL-C, HDL-C and TG. LDL-C (in mmol/L) as reported by the laboratory is calculated using the Friedewald formula: LDL-C = TC – HDL-C – (TG/2.2). Importantly, this formula is invalid for TG $\geq$ 4.5 mmol/L. Direct measurement of LDL-C is available only in certain specialized laboratories. An alternative would be to calculate the non-HDL-C (ie. TC – HDL-C) as a surrogate marker when LDL-C cannot be otherwise evaluated. Fasting plasma lipoprotein electrophoresis and centrifugation allow the evaluation of certain lipid fractions that may be helpful in the diagnosis of disorders such as broad-beta disease or chylomicronaemia.

## CUT-OFF POINTS FOR DYSLIPIDEMIA

*(a) Relevant Lipid Cut-off points*

Lipid cut-off points (Table 1) are guideposts for management and are not absolute, given that lipoprotein concentrations are continuous variables, and therefore the risks for cardiovascular disease do not begin or end with any particular value of lipid.

**Table 1. Cut-off Points for Normal Lipid Levels**

| TOTAL CHOLESTEROL | mmol/L (mg/dL) |
|---|---|
| Desirable | < 5.2 (200) |
| Borderline High | 5.2–6.1 (200–239) |
| High | > 6.2 (240) |
| **LDL CHOLESTEROL** | **mmol/L (mg/dL)** |
| Optimal | < 2.6 (100) |
| Desirable | 2.6–3.3 (100–129) |
| Borderline High | 3.4–4.0 (130–159) |
| High | 4.1–4.8 (160–189) |
| Very High | > 4.9 (190) |
| **HDL CHOLESTEROL** | **mmol/L (mg/dL)** |
| Low | < 1.0 (40) |
| Desirable | 1.0–1.5 (40–59) |
| High | > 1.6 (60) |
| **TRIGLYCERIDES** | **mmol/L (mg/dL)** |
| Optimal | < 1.7 (150) |
| Desirable | 1.7–2.2 (150–199) |
| High | 2.3–4.4 (200–399) |
| Very High | > 4.5 (400) |

These cut-off points aid in the management of the majority of patients, but it should still be stressed that they are essentially guidelines at best. Aggressive management of hyperlipidemia can reduce the risk of clinical events by 25-35%, but leaves about 65-75% under-addressed due to complex multifactorial reasons such as Lp(a), homocysteine, small dense LDL-C, high sensitive C-reactive protein (hsCRP), fibrinogen, procoagulant states and complex interacting factors of the metabolic syndrome for which specific knowledge and therapy are currently at best at the emerging state.

*(b) Selected Updates and Lipid Cut-off points for NCEP III (ATP III)*

- Diabetes mellitus confers an equivalent risk to established CAD
- Defines optimum LDL-C as < 2.6 mmol/L
- Defines optimum TG as < 1.7 mmol/L
- Raises Low HDL-C cutpoint to < 1.0 mmol/L
- Factors non-HDL-C for those with combined hyperlipidemia
- Uses Framingham formula to calculate the 10-year CAD risk for those with > 2 risk factors.

## FREDRICKSON PHENOTYPING

The Fredrickson classification of dyslipidemia is useful in characterizing lipoprotein abnormalities. However, it does not distinguish primary from secondary hyperlipidemia and is not an aetiologic classification. It requires lipoprotein electrophoresis and/or ultracentrifugation with precipitation to separate the lipoprotein fractions for analysis. One of its applications is in determining whether the TG is from dietary (ie. chylomicrons) or endogenous sources (ie. VLDL). It is also useful in diagnosis of familial type III hyperlipidemia or dysbetalipoproteinaemia (broad beta disease). In addition, the nature of the phenotype may suggest the genetics and underlying mechanism in certain cases of primary hyperlipidemias. But it must be emphasized that the establishment of the lipoprotein phenotype does not substitute for making a diagnosis of the underlying aetiology. Also to be noted is that no one phenotypic category is fixed, given that patients can evolve from one phenotype to another over time or during the course of pharmacologic intervention.

**Table 2. Fredrickson Classification of Dyslipidemia based on Phenotype**

| Pheno-type | Lipoprotein Elevated | Plasma Cholesterol | Plasma TG | Athero-genicity | Relative Frequency |
|---|---|---|---|---|---|
| I | Chylomicrons | Normal to ↑ | ↑ ↑ ↑ ↑ | Rare | < 1% |
| IIa | LDL | ↑ ↑ | normal | +++ | 10% |
| IIb | LDL + VLDL | ↑ ↑ | ↑ ↑ | +++ | 40% |
| III | IDL | ↑ | ↑ ↑ ↑ | +++ | < 1% |
| IV | VLDL | Normal to ↑ | ↑ ↑ | + | 45% |
| V | VLDL + Chylomicrons | ↑ to ↑ ↑ | ↑ ↑ ↑ ↑ | + | 5% |

## PRIMARY AND SECONDARY HYPERLIPIDEMIA

By primary hyperlipidemias, we refer to hyperlipidemic disorders characterized by familial transmission with a definite genetic origin in the underlying mechanism. For example, polygenic hypercholesterolemia is a common primary hyperlipidemia with Fredrickson type IIa phenotype facing many clinicians that is due to a yet unknown mode of transmission. Other forms include homozygous and heterozygous familial hypercholesterolemia due to inherited LDL receptor defects, familial chylomicronaemia due to liproprotein lipase/ apo C-II deficiency, familial combined hyperlipidemia, familial dysbetalipoproteinaemia, familial endogenous hypertriglyceridaemia and familial defective apo B-100.

Primary hyperlipidemia should always be suspected in those who present at a very young age. For instance, homozygous familial hypercholesterolemia may even be detected at birth. The significance of making a diagnosis of primary hyperlipidemia is that early intervention can potentially delay the onset of cardiovascular complications and mortality, and family/genetic counselling should be offered to both the affected and their relatives.

Secondary hyperlipidemias are those that are caused by the presence of certain diseases and/or drugs. Common conditions that manifest with hyperlipidemia include the metabolic syndrome, diabetes mellitus, hypothyroidism, Cushing's syndrome, nephrotic syndrome, chronic renal failure, cholestasis and chronic liver disease. Drugs known to lead to hyperlipidemia include oral contraceptives, testosterone, anabolic steroids, glucocorticoids, isotretinoin and protease inhibitors. Although well known to be associated with hyperlipidemia, antihypertensive drugs like beta-blockers and thiazides diuretics usually do not contribute significantly to plasma lipid alterations.

**Table 3. Examples of Primary Dyslipidaemia**

| Selected Disorder of Primary Dyslipidaemia | Fredrickson classification | Genetics and mechanism | Estimated prevalence | Clinical signs, CAD risks Complications |
|---|---|---|---|---|
| Familial chylomicronaemia | I | AR; lipoprotein lipase or apo C-II deficiency | Rare | Lipaemia retinalis, eruptive xanthomas, hepatosplenomegaly, peripheral neuropathy, pancreatitis |
| Familial hypercholesterolemia (FH) | IIa | AD; LDL receptor defect | Homozygote: 1 per million<br>Heterozygote: 1 per 500 | Cutaneous xanthomas, tendon xanthomas, corneal arcus, premature CAD |
| Familial defective apo B-100 | IIa | AD; apo B mutation | Rare | Clinical features resemble heterozygous FH, CAD |
| Polygenic hypercholesterolemia | IIa | Unknown; various genetic defects | High | TC elevation generally less than heterozygous FH |
| Familial combined hyperlipidemia (FCH) | IIa, IIb, IV | Heterogeneous disease of undefined aetiology; overproduction of apo B in most affected | 1 per 100 | No unique clinical features; CAD |
| Familial dysbetalipoproteinaemia | III | AR; apo-E2/E2 linked metabolic defect, usually requiring other metabolic factors for full expression | 1 per 5000 | Palmar xanthomas, tuberoeruptive xanthomas, premature CAD, PVD, stroke |
| Familial endogenous hypertriglyceridaemia | IV | AD; mechanism not known | 1 per 300 | TG typically 2.3–5.6, no chylomicrons |
| Familial mixed hypertriglyceridaemia | V | AD; mechanism not known | Rare | Eruptive xanthomas, lipaemia retinalis, pancreatitis<br>TG > 11.3, HDL-C usually decreased |

## LEARNING POINTS

- Plasma lipids should be screened on all healthy adults above the age of forty. If the results are optimal based on current recommendations for Singapore, screening should be repeated at 3 yearly intervals. The optimal test is a full fasting plasma lipid profile that includes LDL-C, HDL-C and TG
- Cutpoints are helpful in characterizing the severity of the dyslipidemia and they aid decision-making regarding management, but should be used rationally according to the clinical circumstance. The type of dyslipidemia may be determined using the Fredrickson classification, but this does not replace the necessity to determine the aetiology of the dyslipidaemia
- Be on the lookout for primary (genetic) hyperlipidemias, and always keep a healthy suspicion for secondary causes in which the dyslipidemias may improve substantially with control of the underlying disorder or factor.

**RECOMMENDED READING**

1. The International Lipid Information Bureau (ILIB) Lipid Handbook for Clinical Practice. Blood Lipids and Coronary Heart Disease. 2nd Edition. New York, USA. Gotto AM Jr, Assman G, Carmena R, et al. (Eds).
2. 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 2001; 285:2486-97.
3. Clinical Practice Guidelines. Lipids. Singapore: Ministry of Health; 2001.
4. National Health Survey Singapore 1998, Ministry of Health.
5. MOH Clinical Practice Guidelines 6/2003: Health Screening.