Dyslipidemia

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Plasma Lipoproteins

* Lipoproteins are large macromolecular complexes that transport cholesterol and triglycerides (TG) within the blood. They contain a neutral lipid core consisting of TG and cholesterol esters surrounded by a coat composed of phospholipids and specialized proteins known as "apolipoproteins" (see fig. 1).

* Based on density, there are five main classes of lipoproteins: chylomicrons, very low-density lipoproteins (VLDL), intermediate-density lipoproteins (IDL), low-density lipoproteins (LDL) and high-density lipoproteins (HDL). Chylomicrons are the largest and most triglyceride-rich lipoproteins, whereas HDL are the smallest lipoproteins and contain the least amount of lipid (fig. 2).

* Apolipoproteins are required for the structural integrity of lipoproteins and direct their metabolic interactions with enzymes and cell surface receptors. Apolipoprotein A-1 (apo A-1) is a major component of all HDL particles and serves as a marker for this lipoprotein family. Apolipoprotein B (apo B) is the major apolipoprotein for all non-HDL lipoproteins.

Relation of lipoproteins to atherosclerosis:
The association between cholesterol and atherosclerotic disease was reported in multiple large epidemiologic studies such as the Seven Countries Study, the Framingham Study and the Multiple Risk Factor Intervention Trial (MRFIT). The relation between serum cholesterol and subsequent coronary artery disease was found to be continuous, graded and strong (fig. 3). These and many other observational studies formed the basis of the "cholesterol hypothesis" that the relationship between serum cholesterol and atherosclerosis is causal and that reduction of serum cholesterol would reduce atherosclerotic disease.

Measurement of plasma lipids

- A lipoprotein profile involving measurement of triglycerides and indirect calculation of LDL-C (Friedewald formula) requires a 9- to 12-hour fast.
- Blood should be collected in tubes without anticoagulation for serum or with EDTA for plasma.
- Measurement of plasma lipids is preferably performed with the person in a stable condition, that is, in the absence of acute illness including stroke, trauma, surgery, acute infection, weight loss, pregnancy or recent change in diet.
- In persons admitted to the hospital for acute coronary syndromes lipid measurements should be taken on admission or within 24 hours since LDL-C levels begin to decline in the first few hours after a coronary event and are significantly decreased by 24-48 hours.
- LDL-C is routinely estimated from measurements of total cholesterol, total triglycerides and HDL-C in the fasting state by the following formula.
  \[ \text{LDL-C} = \text{TC} - \text{HDL-C} - \frac{\text{TG}}{5} \]
  (TC= total cholesterol; TG= triglycerides)
- For persons with triglycerides over 400 mg/dl, estimation of LDL-C by this method is inaccurate. A more complex ultracentrifugation method in a specialized laboratory is required for accuracy.

Tables (1), (2) and (3) illustrate classification of LDL, total cholesterol and serum triglycerides according to ATP III.

**Etiology of dyslipidemias**

Common causes of "*secondary dyslipidemia*" include:
- Diabetes mellitus
- Nephrotic syndrome
- Chronic renal failure
- Hypothyroidism
- Obstructive hepatobiliary disease
- Drugs... progestins, anabolic steroids, corticosteroids.

Of the "*primary causes*" of dyslipidemia, the most severe forms are caused by "*genetic disorders*" of lipoprotein metabolism.
- **Familial hypercholesterolemia (FH)**
- **Polygenic hypercholesterolemia**
- **Familial combined hypercholesterolemia**.

FH is an autosomal dominant disease with defects in the gene for the LDL receptor. By adulthood the serum cholesterol level in heterozygous FH can be double what it would have been in the absence of the mutation, and typically can be (360-560 mg/dl). In homozygous FH, serum cholesterol levels are almost greater than 600 mg/dl
and can be as high as 1200 mg/dl. Patients with the homozygous form of FH present with tendon xanthomas, corneal arcus, xanthelamate and premature coronary artery disease.

**Management of Dyslipidemias**

Both the 2003 "European guidelines" and "National Cholesterol Education Program- Adult Treatment Panel III: NCEP ATP III" stress that prevention of further progression of coronary heart disease (CHD) in patients with established CHD or other atherosclerotic disease and in asymptomatic healthy individuals should be guided in accordance with "total cardiovascular risk level".

**Cardiovascular Risk assessment:**

A basic principle of prevention is that the "intensity of risk-reduction therapy should be adjusted to a person's absolute risk". Risk assessment requires measurement of LDL cholesterol as part of lipoprotein analysis and identification of accompanying risk determinants.

**Risk determinants in addition to LDL-cholesterol include:**

1. Presence or absence of CHD
2. Other clinical forms of atherosclerotic disease.
3. Other major risk factors other than LDL-C (Table 4).

There are 3 categories of risk that modify LDL-C goals (Table 5).
The category of highest risk consists of CHD and CHD risk equivalents. This category carries a risk for major coronary events equal to that of established CHD i.e. >20% per 10 years (i.e. more than 20 of 100 such individuals will develop CHD or have a recurrent CHD event within 10 years).

CHD risk equivalents comprise (Table 6):
1. Other clinical forms of atherosclerotic disease.
   - Peripheral arterial disease
   - Abdominal aortic aneurysm
   - Symptomatic carotid artery disease
2. Diabetes Mellitus
3. Multiple risk factors (>2 risk factors) that confer a 10-year risk >20%.

Diabetes counts as a CHD risk equivalent because it confers a high risk of new CHD within 10 years, in part because of its frequent association with multiple risk factors. Furthermore, because persons with diabetes who experience a myocardial infarction have an unusually high death rate either immediately or in the long term, a more intensive prevention strategy is warranted.

Method of Risk assessment:
Risk assessment in persons without clinically manifest CHD or other clinical factors of atherosclerotic disease is determined by a 2-step procedure:
1. The number of risk factors is counted (Table 4).
2. For persons with multiple (2+) risk factors, 10-year assessment is carried out with Framingham scoring (appendix) to identify patients whose short term (10-year) risk warrants consideration of intensive treatment. When 0-1 risk factor is present, Framingham scoring is not necessary because 10-year risk rarely reaches levels for intensive intervention.

Framingham scoring divides persons with multiple risk factors (without CHD) or CHD risk equivalents) into three categories
a- >20% - CHD risk equivalent (highest risk)
b- 10-20% - intermediate risk
c- <10% - lowest risk
Suggested New LDL-Cholesterol goals:

In a recent update of ATP III, Grundy S. et al\(^{(4)}\) issued modifications to footnote the ATP III treatment algorithm as follows:

"In high risk patients, the recommended LDL-C goal is <100 mg/dl, but when risk is very high, an LDL-C goal of <70 mg/dl is a therapeutic option. Moreover, when a high-risk patient has high triglycerides or low HDL-C, consideration can be given to combining a fibrate or nicotinic acid with an LDL-lowering drug. For moderately high-risk patients (2+ risk factors and 10-year risk 10% to 20%), the recommended LDL-C goal is <130 mg/dl, but an LDL-C goal <100 mg is a therapeutic option. It is also advised that intensity of therapy be sufficient to achieve at least a 30% to 40% reduction in LDL-C levels". (See fig. 4)

Among factors that place patients at "very high risk" are the presence of established CVD plus

* Multiple major risk factors
* Diabetes mellitus
* Metabolic syndrome
* Patients with acute coronary syndromes

Treatment of Dyslipidemia

The two major modalities of LDL-lowering therapy are
(1) Therapeutic lifestyle changes (TLC)
(2) Drug therapy

Therapeutic lifestyle changes (TLC)- Its essential features are:

* Reduced intake of saturated fats (<7% of total calories) and cholesterol (<200 mg per day)
* Enhancing LDL lowering with plant stanols/sterols (2 g/day) and increased viscous (soluble) fibre (10-25 g/day)
* Weight reduction
* Increased physical activity.

Drug therapy of dyslipidemias

* ATP III continues to identify "elevated LDL-cholesterol as the primary target of cholesterol lowering therapy. For this reason, an LDL-lowering drug should be
started. The usual drug will be a statin, but alternatives are a bile acid sequestrant or nicotinic acid.

* Elevated serum triglycerides are also an independent risk factor for CHD. Factors contributing to elevated triglycerides include: obesity, physical inactivity, cigarette smoking, excess alcohol intake, high carbohydrate diets (>60% of energy intake), several diseases (diabetes, chronic renal failure, nephrotic syndrome), certain drugs (corticosteroids, estrogens, higher doses of beta blockers) and genetic factors.

* Some triglyceride-rich lipoproteins are atherogenic. The latter are called "remnant lipoproteins". In clinical practice, VLDL cholesterol is the most readily available measure of atherogenic remnant lipoproteins.

ATP III identifies the sum of LDL + VLDL cholesterol termed "non-HDL cholesterol" which is equal to total cholesterol minus HDL cholesterol as a "secondary target of therapy" in patients with high triglycerides (>200 mg/dl). The goal for non-HDL cholesterol in persons with high serum triglycerides can be set at 30 mg/dl higher than that for LDL-C on the premise that a VLDL-C level <30 mg/dl is normal.

* Aside from weight reduction and increased physical activity, drug therapy can be considered in high risk persons to achieve the non-HDL cholesterol goal. There are two approaches to drug therapy:
  a- Intensifying therapy with an LDL-lowering drug e.g. uptitration of the dose of a statin.
  b- Adding nicotinic acid or fibrate.

**Low HDL cholesterol**

* Low HDL-C is a strong independent risk factor for CHD. Low HDL-C serves a dual purpose:
  - It modifies the goal for LDL-lowering therapy
  - It is used as a risk factor to estimate 10-year risk for CHD.

* ATP III does not specify a goal for HDL raising. However, in all persons with low HDL-C, the primary target of therapy is to achieve LDL-C goal.

  Second, after LDL goal has been reached, emphasis shifts to weight reduction and increased physical activity (when the metabolic syndrome is present).

  Third, when a low HDL-C is associated with high triglycerides (>200 mg/dl), second priority goes to achieving the non-HDL-cholesterol goal (as outlined above).
Fourth, if triglycerides are <200 mg/dl (isolated low HDL cholesterol), drugs for HDL raising (fibrates or nicotinic acid) can be considered.

**Cost-Effectiveness Issues of Lipid Lowering**

Cost effectiveness is directly related to baseline population risk. As baseline risk increases and effective drug cost decreases cholesterol lowering with statins becomes more cost-effective. LDL-lowering therapy is highly cost-effective in persons with established CAD. It is also cost-effective for primary prevention in persons with CHD risk equivalents. When 10-year risk for hard CHD (myocardial infarction + CHD death) is in the range of 10-20 percent per year, LDL-lowering drug therapy carries an acceptable cost-effectiveness; but when 10-year risk for hard CHD is <10 percent, cost-effectiveness of statins becomes less acceptable. The most cost-effective approach to prevention of CHD should be population intervention: diet modification, exercise and weight control combined with smoking avoidance and cessation.

**References**

Lipoprotein particle structure and its components

Lipoprotein classes and atherosclerosis

Chylomicrons, VLDL, and their catabolic remnants

LDL

HDL

pro-atherogenic

anti-atherogenic

Fig. (1)

Fig. 2
Classification Of LDL-Cholesterol (mg/dl)

- < 100  optimal
- 100-129  near optimal / above optimal
- 130-159  borderline high
- 160-189  high
- ≥ 190  very high

Table(1))

ATP III Lipid and Lipoprotein Classification (continued)

Total Cholesterol (mg/dL)

- <200  Desirable
- 200–239  Borderline high
- ≥240  High

Table(2)

Classification of serum TG

- Normal TG  <150 mg/dl
- Borderline – high TG  150-199 mg/dl
- High TG  200-499 mg/dl
- Very high TG  ≥500 mg/dl

Table(3)
Is Lower Better? Lower Cholesterol Levels are Associated with Lower Mortality Rates

Fig(3)

Major Risk Factors (Exclusive of LDL Cholesterol) That Modify LDL Goals

- Cigarette smoking
- Hypertension (BP ≥140/90 mmHg or on antihypertensive medication)
- Low HDL cholesterol (<40 mg/dL)†
- Family history of premature CHD
  - CHD in male first degree relative <55 years
  - CHD in female first degree relative <65 years
- Age (men ≥45 years; women ≥55 years)

† HDL cholesterol ≥60 mg/dL counts as a “negative” risk factor; its presence removes one risk factor from the total count.

Table(4)
Three Categories of Risk that Modify LDL-Cholesterol Goals

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>LDL Goal (mg/dL)</th>
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<tr>
<td>CHD and CHD risk equivalents</td>
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<td>Multiple (2+) risk factors</td>
<td>&lt;130</td>
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<td>Zero to one risk factor</td>
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Table(5)

CHD Risk Equivalents

- Other clinical forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm, and symptomatic carotid artery disease)
- Diabetes mellitus
- Multiple risk factors that confer a 10-year risk for CHD >20%

Table(6)
NCEP ATP III: LDL-C Goals (2004 proposed modifications)

- **High Risk**
  - CHD or CHD risk equivalents
  - (10-yr risk >20%) (190 -)

- **Moderately High Risk**
  - 1â€’2 risk factors
  - (10-yr risk 10-20%) (160 -)

- **Moderate Risk**
  - 1â€’2 risk factors
  - (10-yr risk <10%) (130 -)

- **Lower Risk**
  - < 2 risk factors
  - Target 160 mg/dL (100 mg/dL)

*Therapeutic option in very high-risk patients and in patients with high TG, non-HDL-C<100 mg/dL; **Therapeutic option; 70 mg/dL = 1.8 mmol/L; 100 mg/dL = 2.6 mmol/L; 130 mg/dL = 3.4 mmol/L; 160 mg/dL = 4.1 mmol/L.

Fig.(4)
Appendix 1

### Estimate of 10-Year Risk for Men

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<tr>
<th>Age</th>
<th>Race</th>
<th>Education</th>
<th>Income</th>
<th>Body Mass Index</th>
<th>Cholesterol</th>
<th>Hypertension</th>
<th>Diabetes</th>
<th>Pack-Years</th>
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