Diabetes and dyslipidemia

Module 22.1

Clinical consequences of dyslipidemia

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Learning Objectives

• To learn the main types of dyslipidemia;
• To learn the consequences of lipid accumulation in different tissues;
• To learn the pathogenesis of atherosclerosis;
• To learn the laboratory evaluation of dyslipidemia;
• To learn the indications for treatment in patients with dyslipidemia;
• To learn the consequences of dyslipidemia in patients requiring nutritional support.

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Key Messages

• Dyslipidemia is important due to its causal relation with atherosclerosis and cardiovascular disease;
• Plasma lipid concentrations are stratified according to the presence of different cardiovascular risk factors in an individual and may differ between different subjects;
• The traditional classification of hyperlipidemia is based on the pattern of plasma lipoprotein elevation as observed in lipoprotein electrophoresis. However, most current clinical guidelines on hyperlipidemia management are not based on electrophoresis results;
• Hyperlipidemia may be divided into primary and secondary disorders. In the first case, genetic defects alter normal metabolism of lipoproteins. Other factors that modify lipoprotein metabolism, such as diabetes mellitus, increase lipoprotein concentrations in secondary hyperlipidemia. Many patients suffer both primary genetic disorders and secondary causes: the primary genetic defect predisposes them to a more severe expression of the secondary lipid disorder associated with underlying pathologies such as obesity and diabetes;
• Elevated plasma lipids (cholesterol or triglycerides) can accumulate in macrophage reticuloendothelial cells in certain tissues. The clinical expression may be as Xanthelasmas, Tendon, Tuberous, Palmar, and Eruptive Xan Thom as;
• Serum triglyceride concentrations exceeding 1000 mg/dL (11 mmol/L) may precipitate attacks of acute pancreatitis. The pathogenesis of hypertriglyceridemic pancreatitis is unclear, but the release of free fatty acids may damage pancreatic acinar cells or capillary endothelium;
Abnormalities in plasma lipoproteins are well known risk factors for atherosclerosis;

Atherosclerosis preferentially affects various regions of the circulation with distinct clinical manifestations depending on the particular circulatory bed affected;

The development of the atheromatous plaque involves fatty streak formation, lipoprotein oxidation, leukocyte recruitment, foam cell formation, smooth-muscle cells migration, microthrombi formation and calcification, vascular remodelling, plaque instability and rupture, and endothelial dysfunction;

Clinical Guidelines recommend cholesterol screening for primary prevention of coronary heart disease starting in adults at 20 to 45 years depending on the particular guideline. Individuals should have a fasting lipid profile done every 5 years. It includes total cholesterol, cLDL, cHDL and triglycerides. Non-HDL cholesterol (total cholesterol minus HDL cholesterol) measures all cholesterol particles that are considered atherogenic and it has been proposed as a useful index;

Recommendations on when to start medical therapy depend on LDL levels and on other risk factors for CHD as well. Different organizations have established guidelines that vary slightly. They usually follow a step-based approach to individual risk assessment;

Total parenteral nutrition (TPN) may alter plasma lipids and it is therefore important to monitor plasma lipids, particularly in those patients who have a lipid abnormality. The phospholipid-to-triglyceride ratio of the intravenous fat emulsion has an influence on lipid metabolism. Other factors to be considered are glucose overload, sepsis, multiorgan failure, obesity, diabetes, liver disease, renal failure, and history of hyperlipidemia, pancreatitis, and certain medications;

If hypertriglyceridemia occurs, the dextrose or lipid dosage is reduced, depending on the cause. It may be necessary to withhold daily lipid infusion when the serum is lipemic or when serum triglyceride concentrations exceed 400 mg/dL. To prevent essential fatty acid deficiency, 3-5% of total caloric intake should be as linoleic acid. In adult patients that can be achieved giving 60 g of IV lipids twice weekly.
1. Definition

The term dyslipidemia (DLP) designates different alterations of plasma lipids, including an increase in total cholesterol, cholesterol transported by low density lipoprotein (cLDL) and triglycerides, as well as a decrease of cholesterol transported by high density lipoprotein (cHDL). This term is slightly broader than hyperlipidemia (HLP) which refers only to an increase of plasma concentrations of cholesterol and triglycerides. Actually, hyperlipidemia is synonymous with hyperlipoproteinemia. This may be due either to increased production or secretion of lipids into the circulation or to decreased clearance or removal from the circulation; in some cases, both processes coexist. These alterations may affect one or more classes of lipoproteins.

DLP is important due to its causal relation to atherosclerosis and cardiovascular disease (CVD), which are the major causes of death and disability in Europe. More women than men die from CVD, 2.3 millions vs 2 millions, respectively. There are important regional differences with reduced prevalence in Western countries of Europe (1).

The cut-off point defining a particular lipid concentration as high has several interpretations. From an epidemiological point of view, HLP may be defined as a value over a particular percentile from population distributions, for example, the 90th to 95th percentile. However, from a clinical point of view, lipoproteins within the low normal or ideal (desirable) range, has the best association with the prevention of cardiovascular disease or to therapeutical benefit from lipid lowering drugs. Measurements which include concentrations of cLDL, cHDL and, to a lesser degree, triglycerides, are preferable to total cholesterol alone. High or low cLDL or cHDL, respectively, are directly and causally linked to an increased coronary risk.

The desirable plasma concentrations are stratified according to the presence of other cardiovascular risk factors in an individual and may therefore vary between different subjects. However, it is widely accepted that coronary risk increases with higher lipids across the complete range of values, with decreased risk as these values descend.

2. Classification

The pattern of plasma lipoprotein elevation is useful to classify HLP. The Fredrickson classification has been very helpful to understand lipid disorders (Table 1) and some denominations of DLP are still based on the predominant pattern of lipoprotein elevation. However, this classification is based on electrophoresis of plasma lipoproteins, but although it has been used for many years, it has now fallen into disuse. This is due to the fact, on the one hand, that different lipoprotein patterns may occur in several family members with the same disorder and on the other hand, that most current managing clinical guidelines are not based on electrophoresis results.

Table 1 Classification of hyperlipidemia according to Fredrickson

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Increased Lipoprotein</th>
<th>Plasmatic Cholesterol</th>
<th>Plasmatic Triglycerides</th>
<th>Atherogenesis</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Chyomicrons</td>
<td>Normal or ↑</td>
<td>↑↑↑↑</td>
<td>+</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>IIa</td>
<td>LDL</td>
<td>↑↑</td>
<td>Normal</td>
<td>+++</td>
<td>10</td>
</tr>
<tr>
<td>IIb</td>
<td>LDL &amp; VLDL</td>
<td>↑↑</td>
<td>↑↑</td>
<td>+++</td>
<td>45</td>
</tr>
<tr>
<td>III</td>
<td>ILD</td>
<td>↑↑</td>
<td>↑↑↑↑</td>
<td>+++</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>IV</td>
<td>VLDL</td>
<td>Normal or ↑</td>
<td>↑↑</td>
<td>+</td>
<td>45</td>
</tr>
<tr>
<td>V</td>
<td>VLDL &amp; chyomicrons</td>
<td>↑↑</td>
<td>↑↑↑↑</td>
<td>+</td>
<td>&lt; 1</td>
</tr>
</tbody>
</table>

HLP may be divided into primary disorders (Table 2), in which genetic defects cause abnormal lipoprotein metabolism, and secondary disorders, in which acquired conditions (Table 3), such as obesity and diabetes, modify lipoprotein metabolism. Many patients suffer a combination of both primary genetic and secondary causes: the primary genetic defect predisposes them to a more severe expression of the secondary lipid disorder associated with third acquired pathology. At the same time, correction of the underlying disorder causing the secondary process also benefits the treatment of the primary genetic defect. In clinical practice, as shown in Table 2, it is useful to...
focus on the main plasma lipid disorder, either raised cholesterol, triglycerides, or both, to orientate the management of the patients (2).

Table 2 Classification of hyperlipidemia according to main lipid disorder

<table>
<thead>
<tr>
<th>Type</th>
<th>Mutant gene</th>
<th>Inheritance</th>
<th>Prevalence</th>
<th>Increased Lipoprotein</th>
<th>Cardiovascular risk</th>
<th>Signs &amp; Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Isolated Hypercholesterolemia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polygenic Hypercholeste rolemia</td>
<td>Unknown</td>
<td>Unknown</td>
<td>5/100</td>
<td>LDL</td>
<td>High</td>
<td>IC</td>
</tr>
<tr>
<td>Familial Hypercholeste rolemia</td>
<td>LDL receptor</td>
<td>AD</td>
<td>1/500</td>
<td>LDL</td>
<td>High</td>
<td>IC Tendinous Xanthoma Xanthelasma</td>
</tr>
<tr>
<td>Familial defective Apo B-100</td>
<td>Apo B</td>
<td>AD</td>
<td>1/1000</td>
<td>LDL</td>
<td>High</td>
<td>Tendinuous Xanthoma</td>
</tr>
<tr>
<td>Familial combined hyperlipidemia</td>
<td>Unknown</td>
<td>AD</td>
<td>1/100</td>
<td>LDL &amp; VLDL</td>
<td>High</td>
<td>IC</td>
</tr>
<tr>
<td><strong>Isolated Hypertriglyceride-mia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Familial deficit of LPL</td>
<td>LPL</td>
<td>AR</td>
<td>1/10³</td>
<td>Q</td>
<td>?</td>
<td>Eruptive Xanthoma Pancreatitis</td>
</tr>
<tr>
<td>Familial deficit of apoC-II</td>
<td>ApoC-II</td>
<td>AR</td>
<td>1/10³</td>
<td>Q</td>
<td>?</td>
<td>Eruptive Xanthoma Pancreatitis</td>
</tr>
<tr>
<td>Familial combined hyperlipidemia</td>
<td>Unknown</td>
<td>AD</td>
<td>1/1000</td>
<td>LDL &amp; VLDL</td>
<td>High</td>
<td>IC</td>
</tr>
<tr>
<td>Familial hyptriglycerid emia</td>
<td>Unknown</td>
<td>AD</td>
<td>0,5-1/100</td>
<td>VLDL &amp; Q</td>
<td>Normal/ high</td>
<td>Pancreatitis IC</td>
</tr>
<tr>
<td><strong>Mixt Hyperlipidemia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Familial Dysbetalipoproteinemia-mia</td>
<td>ApoE</td>
<td>AR (AD rare)</td>
<td>1/10⁴</td>
<td>IDL &amp; RQ</td>
<td>High</td>
<td>Palmar and tuberous Xanthomas</td>
</tr>
<tr>
<td>Familial combined hyperlipidemia</td>
<td>Unknown</td>
<td>AD</td>
<td>1/1000</td>
<td>LDL &amp; VLDL</td>
<td>High</td>
<td>IC</td>
</tr>
</tbody>
</table>

Table 3 Clinical Disorders associated with Secondary Hyperlipidemia

<table>
<thead>
<tr>
<th>Endocrine Disorders</th>
<th>Non Endocrine Disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus</td>
<td>Alcohol</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Nephrotic syndrome</td>
</tr>
<tr>
<td>Estrogen therapy</td>
<td>Uremia</td>
</tr>
<tr>
<td>Glucocorticoid therapy</td>
<td>Biliary obstruction or cholestasis</td>
</tr>
<tr>
<td>Hypopituitarism</td>
<td>Hepatitis</td>
</tr>
<tr>
<td>Acromegaly</td>
<td>Systemic lupus erythematosus</td>
</tr>
<tr>
<td>Anorexia nervosa</td>
<td>Monoclonal gammopathy</td>
</tr>
<tr>
<td>Lipodystrophy (congenital or acquired)</td>
<td>Acute intermittent porphyria</td>
</tr>
<tr>
<td>Werner's syndrome</td>
<td>Glycogen storage disease</td>
</tr>
</tbody>
</table>
3. Clinical manifestations

Most patients with DLP are initially asymptomatic, although some of them show skin abnormalities, develop pancreatitis or have clinical manifestations of atherosclerosis, such as hypertension, coronary heart disease, cerebrovascular disease and peripheral artery disease.

3.1 Skin

Elevated plasma lipids (cholesterol or triglycerides) can accumulate in macrophage reticuloendothelial cells in certain tissues, particularly skin, tendons, eye, liver, and spleen.

**Xanthelasmas** are small, raised, yellowish macules that typically appear on or near the eyelids. Occasionally, they also occur in patients with normal plasma cholesterol levels, possibly as the result of abnormal uptake of lipoproteins by tissue macrophages. Xanthelasmas may regress when therapy decreases cholesterol concentrations. They are seen in familial hypercholesterolemia, familial defective apo-B100, and type III hyperlipoproteinemia.

**Tendon xanthomas** are nodular accumulations of cholesterol that are deposited in tissue macrophages of different tendons, particularly Achilles tendon and extensor tendons in the hands, knees, elbows and buttocks. They may be small and therefore detailed examination is needed to avoid overlooking them. They appear in the HLP mentioned just before, but they are particularly common in familial hypercholesterolemia.

**Tuberous xanthomas** are subcutaneous nodules that develop in the skin over areas predisposed to repeated trauma such as the elbows and knees. The size may be variable, as well as their number in a singular location. These xanthomas are most often seen in type III hyperlipoproteinemia and also occur in familial hypercholesterolemia.

**Palmar xanthomas** are cutaneous deposits in the palmar and digital creases of the hands. This type of xanthoma is very characteristic of type III hyperlipoproteinemia and high plasma levels of β-VLDL.

**Eruptive xanthomas** are deposits of triglycerides in dermal histiocytes predominantly distributed in the abdominal wall, the back, the buttocks, and other pressure contact areas. They appear as small, yellowish, round papules with a pale centre and erythematous base. When they are visible, plasma triglyceride level is high (over 1000 mg/dl or 11.3 mmol/L). As triglyceride levels fall with treatment, these xanthomas tend to vanish. They also appear in patients with LPL deficiency (2).

3.2 Eye

**Corneal Arch**: it is an arc-shaped corneal deposit of cholesterol. It is characteristic of familial hypercholesterolemia, but it also appears in normal individuals older than 45 years. Therefore, its presence is not pathognomonic.

**Lipemia retinalis**: retinal vessels appear creamy white or yellowish. This funduscopic finding occurs only with extreme hypertriglyceridemia, i.e. exceeding 4000 mg/dl. This sign appears in patients with familial deficiency of LPL or Apo C-II.

3.3 Pancreatitis

After gallstones and alcoholism, hypertriglyceridemia is the third most common identifiable, noniatrogenic cause of acute pancreatitis, causing around 5% of all cases. Serum triglyceride concentrations exceeding 1000 mg/dL (11 mmol/L) may precipitate such attacks of acute pancreatitis, although the pathogenesis is unclear. It is possible that the release of free fatty acids may damage pancreatic acinar cells or capillary endothelium.

The association between hypertriglyceridemia due to inherited lipid disorders and acute pancreatitis can occur in early childhood, particularly in children who are homozygous for lipoprotein lipase or apolipoprotein C-II (apo C-II) deficiency.

Most adults with hyperchylomicronemia have a mild form of genetically inherited type I or type V hyperlipoproteinemia and an additional condition known to raise serum lipids (e.g., alcohol abuse,
obesity, insulin resistance, diabetes mellitus, hypothyroidism, pregnancy, estrogen, tamoxifen therapy, glucocorticoid excess, nephrotic syndrome, or beta-blocker therapy).

Several patterns of hypertriglyceridemia-induced pancreatitis have been described (3). The first is a patient with poorly controlled diabetes and a history of hypertriglyceridemia; treatment with insulin corrects the elevated levels of triglycerides. The second is an alcoholic patient who is found to have hypertriglyceridemia on hospital admission. Alcohol causes a moderate rise in serum triglyceride concentration in a “dose-dependent” manner. Alcoholic patients with severe hyperlipidemia often have a coexisting primary genetic disorder of lipoprotein metabolism (4). The third is a nondiabetic, nonalcoholic, nonobese person who has drug- or diet-induced hypertriglyceridemia. Drug-induced disease is more likely to occur if there is underlying hypertriglyceridemia (5).

The clinical manifestations of hypertriglyceridemia-associated disease are similar to those of other causes of acute pancreatitis: abdominal pain, nausea, and vomiting are the major symptoms. However, the serum amylase concentration may not be substantially elevated at presentation (6).

3.4 Cardiovascular disease

Abnormalities in plasma lipoproteins are well known risk factors for atherosclerosis. It is the leading cause of death and disability in the developed world. Central to the pathogenesis of atherosclerosis is the deposition of cholesterol in the arterial wall. Nearly all lipoproteins are involved in this process. Low-density lipoprotein (LDL), particularly the small, dense form, is considered the main culprit, followed by remnant lipoprotein and very-low-density lipoprotein (VLDL). When HLP occurs in combination with other risk factors early cardiovascular disease is commonplace.

Atherosclerosis preferentially affects various regions of the circulation with distinct clinical manifestations depending on the particular circulatory bed affected: angina pectoris and myocardial infarction, strokes and transient cerebral ischemia, peripheral arterial disease leading to intermittent claudication and gangrene, mesenteric ischemia and renal artery stenosis.

Atherosclerosis manifests itself focally not only in space, but in time as well. Atherosclerotic plaques grow discontinuously with quiescent periods followed by others with more rapid progression. Clinical expressions of atherosclerosis mirror this time frame. They may be chronic, as in stable, effort-induced angina pectoris or intermittent claudication. Alternatively, the presence of atherosclerosis may be revealed by an acute clinical event such as myocardial infarction or cerebrovascular accident. On the other hand, atherosclerosis may be a post mortem finding without any prior clinical manifestation (7).

The development of the atheromatous plaque has been comprehensively studied. The main steps are (7, 8, 9):

- Fatty streak formation: Hypercholesterolemia promotes accumulation of LDL particles in the intima of the vascular wall. The lipoprotein particles often associate with constituents of the extracellular matrix;
- Lipoprotein oxidation: Lipoproteins in the intima are separated from plasma antioxidants and are altered by oxidative modification. In patients with diabetes nonenzymatic glycation of lipoproteins and other matrix proteins may contribute to the development of the plaque;
- Leukocyte recruitment: Oxidized lipoproteins may elicit a local inflammatory response that generates different molecular signals that attract lymphocytes and monocytes to the site of the accumulation of LDL particles. These cells and vascular wall cells produce adhesion molecules that maintain the attraction of leucocytes to the nascent plaque;
- Foam cell formation: The mononuclear phagocytes in the evolving fatty streak differentiate into macrophages. They multiply and exhibit increase expression of receptors for modified lipoprotein. Therefore, these cells acquire a scavenger role. They accumulate lipids and are transformed into foam cells, in which lipid droplets are deposited in the cytoplasm;
- Smooth-muscle cell migration: some of these cells travel to the atherosclerotic lesion and accumulate within the expanding intima. They are subjected to positive and negative stimuli from different proinflammatory cytokines, synthesized by local macrophages and vascular wall cells. The usual outcome is that migrated cells produce increased amounts of extracellular matrix that expands the intima and leads to the advanced atherosclerotic lesion. Fibrous tissue accumulates in the fatty streak;
• Associated factors: various diseases and hormones may contribute to the development of the atheromatous plaque: diabetes mellitus, hypertension, smoking, sexual hormones, proteins related to coagulation and fibrinolysis, such as plasminogen-activator inhibitor 1 (PAI-1) and lipoprotein (a);

• Microthrombi: In advanced fatty streaks limited endothelial denudation occurs. The extracellular matrix is very thrombogenic. Platelets are attracted to these microscopic breaches in endothelial integrity and microthrombi are organized in such sites. Activated platelets release numerous factors that can promote the fibrotic response. However, these microthrombi may be clinically silent due to local fibrinolysis and endothelial repair;

• Mineralization: Advanced atheroma plaques may accumulate calcium. Osteocalcin, osteopontin and bone morphogenetic proteins are involved in bone formation and in atherosclerotic plaques as well;

• Plaque evolution: The atherosclerotic plaque development is not linear, but is punctuated by contradictory events, such as import and export of lipoproteins and inflammatory cells, proliferation and apoptosis of smooth-muscle cells, deposition and remodelling of extracellular matrix, etc. Late lesions are more fibrous, while initial lesions are more cellular;

• Plaque-vessel relationship: Vessels affected by atherogenesis tend to increase in diameter, a phenomenon known as compensatory enlargement, a type of vascular remodelling. Initially, the plaque usually grows outward and therefore does not represent an obstacle to flow through the vessel thereby decreasing tissue perfusion. Eventually, the plaque causes flow-limiting stenosis that may be manifest as exercise-dependent ischemia, for example angina pectoris or intermittent claudication (10, 11);

• Plaque instability and rupture: Acute cardiovascular events are frequently triggered by a non-occlusive plaque that has not previously caused chronic symptoms of ischemia, but has become unstable. Either a fracture in the plaque or a superficial erosion of the endothelium initiates the coagulation cascade and prompt the development of a thrombus. Consequently, the vessel’s lumen is blocked by the thrombosis and the blood flow is severely limited. It has been proved that unstable plaques contain more lipids and inflammatory cells, but less smooth-muscle cells than stable ones. This is probably due to an ongoing inflammatory response at sites of plaque rupture. The more local inflammation the less extracellular matrix and fibrous tissue, facilitating the rupture (12).

• Endothelial dysfunction: Disordered endothelial vasomotor function of the coronary arteries is common in patients with angina and results in diminished vasodilatation or even vasoconstriction in response to various stimuli, including exercise.

4. Management of dyslipidemia

The management of dyslipidemia exceeds the scope of this Module in the LLL programme, but we will briefly review the laboratory evaluation and the goals of treatment.

4.1 Laboratory evaluation of dyslipidemia

Several Scientific Societies have issued guidelines with recommendations for hyperlipidemia screening. The National Cholesterol Education Program’s (NCEP) Coordinating Committee have published the Adult Treatment Panel (ATP) III guideline on the detection, evaluation, and treatment of hyperlipidemia (13). These guidelines state that adults aged 20 years and older should have a fasting lipid profile done every 5 years. Other scientific societies as the American College of Physicians, the American Academy of Family Physicians and the US Preventives Services Task Force recommend cholesterol screening for primary prevention of CHD at 35 years and 45 years, for men and women respectively (14).

The fasting profile includes total cholesterol, cLDL, cHDL and triglycerides. If it is impossible to obtain fasting levels, then only the total cholesterol and HDL provide reliable information. The definite results of these tests have to be evaluated along with the other risk factors in each individual. Special tests, such as C-reactive protein (CRP) measurement, can be considered to define a subset of patients that is at excess risk for Coronary Heart Disease (CHD) (15). If a patient is at average risk for a lipid-related event over the next 1 to 2 years, laboratory tests should be repeated every 1 to 2 years, because total cholesterol and LDL tend to increase with age. If a patient, due to his or her risk stratification, needs drug therapy, before starting it, he/she would have measured baseline liver function tests (LFTs), creatinine kinase (CK) and thyrotropin (TSH).
Follow-up tests should include LFTs 6 to 12 weeks after initiation of therapy, every 6 months for 1 year, and on a yearly basis thereafter. CK should be monitored if indicated by symptoms, but routine periodic retesting is not recommended (16).

Other measurements are being considered as emerging or potential risk factors for CHD (14):

Non-high-density lipoprotein cholesterol or Non-HDL cholesterol (total cholesterol minus HDL cholesterol) measures all cholesterol particles that are considered atherogenic. In ATP III guidelines, non-cHDL should have an upper limit just 30 mg/dL higher than the goal for cLDL. In these guidelines, non-cHDL is a secondary target of therapy in patients with triglycerides over 200 mg/dL.

Total-to-high-density lipoprotein-cholesterol ratio may be more predictive of CHD than total cholesterol or LDL cholesterol. Among men, a ratio of 6.4 or greater was associated with greater risk of CHD than the individual parameters mentioned.

Lipoprotein (a) or Lp (a) consists of an apoprotein (a) molecule bound by a sulphydryl link to the apolipoprotein B moiety of an LDL particle. Apoprotein (a) has homology with plasminogen and may inhibit fibrinolysis by competing with plasminogen. Elevated Lp (a) levels predict CHD events, particularly in patients with dyslipidemia or low cHDL.

Small, dense low-density lipoprotein particles are associated with increased serum concentrations of apo B and triglycerides and reduced serum HDL. Epidemiological studies have noted an association between small, dense LDL and CHD. However, routine screening for LDL particle size or concentration has not been validated.

Apolipoproteins B and apo A-I: apolipoproteins may be a better indicator of atherogenicity. However, in clinical practice these are not much better than measurements of cholesterol fractions. In a recent study more than 3300 middle-aged, white participants in the Framingham Offspring Study without cardiovascular disease were followed for a median of 15 years. A total of 291 first CHD events occurred, 198 of them in men and 93 in women. In men, elevations in non-HDL cholesterol, apo B, total cholesterol:HDL ratio, LDL:HDL ratio, and apo B:apo A-1 ratio were all significantly associated with increased CHD risk to a similar degree. Elevated apo A-1 and HDL were likewise associated with reduced CHD risk. In men, total cholesterol:HDL and apo B:apo A-1 ratios both improved reclassification of 10-year risk for CHD; however, the difference between the two was not significant. In women, neither lipid ratio improved CHD risk reclassification. The authors concluded that the overall performance of apo B:apo A-I ratio for prediction of CHD was comparable with that of traditional lipid ratios but did not offer incremental utility over total cholesterol:HDL-C. These data do not support measurement of apo B or apo A-I in clinical practice when total cholesterol and HDL-C measurements are available (17). However, a recent study done in 52 countries, the INTERHEART study, has reported that the non-fasting ApoB/ApoA1 ratio was superior to any of the cholesterol ratios for estimation of the risk of acute myocardial infarction in all ethnic groups, in both sexes, and at all ages, and the authors claim that it should be introduced into worldwide clinical practice (18).

4.2 Selection of patients for treatment
Elevated LDL is associated clearly with an increased risk for cardiovascular disease. Recommendations on when to start medical therapy depend on LDL levels and on other risk factors for CHD as well. Different organizations have established guidelines that vary slightly. The NCEP ATP III guideline is the most widely used set of recommendations, particularly in U.S.A. The ATP III follows a step-based approach to individual risk assessment (19). It is useful to assign an individual’s risk for CHD and serves as the basis for future treatment decisions. In the ATP III a patient’s 10-year risk for CHD is verified, and the patient’s risk category determines treatment goals for LDL. Patients are categorized as high risk (> 20% risk for CHD in 10 years), moderate risk (10%-20%), or low risk (< 10%). The main steps are:

- Obtain a fasting lipid profile, including cholesterol, LDL, HDL, and triglyceride levels (Table 4);
Table 4 ATP III Classification of LDL, Total, and HDL Cholesterol (mg/dL)

<table>
<thead>
<tr>
<th>LDL Cholesterol</th>
<th>Primary Target of Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 100</td>
<td>Optimal</td>
</tr>
<tr>
<td>100-129</td>
<td>Near optimal/above optimal</td>
</tr>
<tr>
<td>130-159</td>
<td>Borderline high</td>
</tr>
<tr>
<td>160-189</td>
<td>High</td>
</tr>
<tr>
<td>&gt;190</td>
<td>Very high</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Total Cholesterol</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 200</td>
<td>Desirable</td>
</tr>
<tr>
<td>200-239</td>
<td>Borderline high</td>
</tr>
<tr>
<td>&gt;240</td>
<td>High</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HDL Cholesterol</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 40</td>
<td>Low</td>
</tr>
<tr>
<td>&gt;60</td>
<td>High</td>
</tr>
</tbody>
</table>

- Identify presence of clinical atherosclerotic disease that confers high risk for coronary heart disease (CHD) events (CHD risk equivalent):
  - Clinical CHD; Symptomatic carotid artery disease; Peripheral arterial disease; Abdominal aortic aneurysm;
- Determine presence of major risk factors (other than LDL):
  - 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.
- If two or more risk factors are present, the patient’s 10-year risk for CHD is estimated by using the Framingham scoring system. This system looks at age, total cholesterol, HDL cholesterol, blood pressure, and cigarette smoking. Individuals are stratified in three levels according to the 10-year risk:
  - >20% – CHD risk equivalent;
  - 10-20%;
  - <10%;
- Depending on risk category, establish LDL goal of therapy, determine LDL level at which to initiate Therapeutic Lifestyle Changes and at which to consider drug therapy (Table 5);

Table 5 ATP III Classification of Risk Categories, LDL goal and LDL level at which initiate therapeutic interventions.

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>LDL Goal</th>
<th>LDL Level at Which to Initiate Therapeutic Lifestyle Changes (TLC)</th>
<th>LDL Level at Which to Consider Drug Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD or CHD Risk Equivalents # (10-year risk &gt;20%)</td>
<td>&lt;100 mg/dL</td>
<td>&gt;100 mg/dL</td>
<td>&gt;130 mg/dL (100-129 mg/dL: drug optional)*</td>
</tr>
<tr>
<td>2+ Risk Factors (10-year risk &lt;20%)</td>
<td>&lt;130 mg/dL</td>
<td>&gt;130 mg/dL</td>
<td>10-year risk 10-20%: &gt;130 mg/dL 10-year risk &lt;10%: &gt;160 mg/dL</td>
</tr>
<tr>
<td>0-1 Risk Factor†</td>
<td>&lt;160 mg/dL</td>
<td>&gt;160 mg/dL</td>
<td>&gt;190 mg/dL (160-189 mg/dL: LDL-lowering drug optional)</td>
</tr>
</tbody>
</table>

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Recent trials suggest that optimal LDL levels may be even lower (less than 70 mg/dL) for the very high risk patients (1). Patients at very high risk include those with established cardiovascular disease plus:
- Multiple major risk factors, especially diabetes mellitus
- Severe and poorly controlled risk factors, especially continued cigarette smoking
- Multiple risk factors of the metabolic syndrome
- Acute coronary syndromes

* The use of LDL-lowering drugs in this category is recommended if an LDL cholesterol <100 mg/dL cannot be achieved by therapeutic lifestyle changes. Alternatively, drugs that primarily modify triglycerides and HDL, e.g., nicotinic acid or fibrates, may also be selected. Clinical judgment also may call for deferring drug therapy in this subcategory.

† Almost all people with 0-1 risk factor have a 10-year risk <10%, thus 10-year risk assessment in people with 0-1 risk factor is not necessary.

- Initiate therapeutic lifestyle changes (TLC) if LDL is above goal;
- Consider adding drug therapy if LDL exceeds levels shown in Step 5 table: Consider drug simultaneously with TLC for CHD and CHD equivalents or adding drug to TLC after 3 months for other risk categories;
- Identify metabolic syndrome and treat, if present, after 3 months of TLC;
- Treat elevated triglycerides (≥ 150 mg/dL) (Table 6): The primary aim of therapy is to reach LDL goal. Next, patients should intensify weight management and increase physical activity. If triglycerides are >200 mg/dL after LDL goal is reached, set secondary goal for non-HDL cholesterol (total - HDL) 30 mg/dL higher than LDL goal.

Table 6 ATP III Classification of Serum Triglycerides mg/dL

<table>
<thead>
<tr>
<th>Concentration</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;150</td>
<td>Normal</td>
</tr>
<tr>
<td>150-199</td>
<td>Borderline high</td>
</tr>
<tr>
<td>200-499</td>
<td>High</td>
</tr>
<tr>
<td>500</td>
<td>Very high</td>
</tr>
</tbody>
</table>

The European approach to cardiovascular prevention is slightly different, although they share similar goals of controlling risk factors. A mnemonic rule has been developed as “European heart telephone number 035140530, which represent:
- 0 No tobacco;
- 3 walk 3 km daily or 30 mins any moderate activity;
- 5 portions of fruit and vegetables a day;
- 140 (mm Hg) Systolic Blood Pressure;
- 90 (mm Hg) Diastolic Blood Pressure;
- 5 (mmol/L) total cholesterol;
- 3 (mmol/L) LDL cholesterol;
- 0 Avoidance of overweight and diabetes.

Since 2003 the European Guidelines on cardiovascular disease have replaced the Framingham model by a new European risk prediction system known as SCORE (20). It was developed using data from 12 European cohort studies (N = 205,178), from a wide geographic distribution of countries at different levels of cardiovascular risk, including around 3 million person-years of observation and more than 7000 fatal cardiovascular events. It addresses fatal events rather than total events, total cardiovascular risk rather than just CHD, charts for cholesterol and cholesterol: HDL ratio, and includes more detail for the 50- to 65-year age range (21).

It is believed that this prediction system is more adjusted to the European populations that the Framingham score, which could attribute an excess of risk in these populations. In SCORE model risk estimation is based on age, sex, smoking habits, systolic blood pressure (SBP), and either total cholesterol or cholesterol/HDL ratio. There are two sets of SCORE charts: the low-risk chart is for countries such as Belgium, France, Greece, Italy, Luxembourg, Portugal, Spain, and Switzerland. The high-risk chart is for use in all other European countries. Relative risk is calculated by comparing an individual’s risk category with that of a nonsmoking person of the same age and gender with blood pressure < 140/90 mm Hg and total cholesterol < 5 mmol/L (< 190 mg/dL).
CVD risk assessment identifies two groups. The first group includes those individuals at high risk, because they have known CVD, or diabetes mellitus 2 and diabetes mellitus type 1 with microalbuminuria, or very high levels of individual risk factors. Patients with familial hypercholesterolemia with levels of cholesterol over 8 mmol/L (320 mg/dl) and LDL cholesterol > 6 mmol/L (240 mg/dl) are at high total risk of CVD. In that case, assessment of total risk is not necessary. For all other people, the SCORE risk charts can be used to estimate total risk. Many people have mildly raised levels of several risk factors that in combination can result in high levels of total CVD risk.

For high risk individuals the objectives are total cholesterol < 4.5 mol/l (175 mg/dl), with an option of 4 mmol/L (155 mg/dl) if feasible, and LDL cholesterol < 2,5 mmol/L (100 mg/dl), with an option of 2 mmol/L (80 mg/dl) if feasible. If these goals are not feasible, total risk can still be reduced by means of increase efforts to control other risk factors. These goals usually require drug therapy along with lifestyle intervention.

In individuals with SCORE > 5 %, lifestyle recommendations are proposed for 3 months. If they do not reduce SCORE to < 5 %, the goals are total cholesterol < 4.5 mol/l (175 mg/dl) and LDL cholesterol < 2.5 mmol/L (100 mg/dl), similar to high risk individuals, and drug therapy should be considered. For individuals with SCORE < 5 %, the goals are cholesterol < 5 mmol/L (190 mg/dl) and LDL cholesterol should be < 3 mmol/L (115 mg/dl).

No specific treatment goals are defined for HDL cholesterol and triglycerides, but concentrations of HDL cholesterol < 1 mmol/L (40 mg/dl) in men and < 1.2 mmol/L (45 mg/dl) in women, and similarly, fasting triglycerides > 1.7 mmol/L (150 mg/dl), serve as markers of increased cardiovascular risk. Values of HDL cholesterol and triglycerides should also be used to guide the choice of drug therapy (22).

Treatment with statins to reduce cholesterol levels has been proven beneficial in patients who have CHD, particularly in those who had hyperlipidemia, but even patients with normal lipid levels have been shown to obtain some benefit. It is understandable that patients who are at highest risk for CHD or recurrent cardiovascular events will benefit most from pharmacologic therapy.

In the case of elderly patients there has been more controversy. The bottom line is that functional status should be given more importance than chronological age. Cardiovascular disease is a frequent cause of death among the elderly. It has been suggested that elderly patients will receive primary prevention if they have two or more cardiac risk factors and LDL cholesterol greater than 160 mg/dl.

Patients with diabetes, even without clinical cardiovascular disease, are considered at high risk and have the same level of recommendations as CHD patients.

Low HDL has been recognized recently as a strong independent predictor of CHD. In patients with low HDL and high LDL levels, LDL remains the primary goal of therapy. In patients with low HDL and high triglycerides, non-HDL cholesterol becomes the second priority. In patients with isolated low HDL, drugs for raising HDL can be considered in patients at high risk for CHD. Fibrates or a combination of statin plus niacin may be tried. Torcetrapib, a cholesterol ester transfer protein (CETP) inhibitor, may increase HDL. However it was withdrawn by the manufacturer just before being launched, due to adverse events (23, 14).

5. Nutritional support and dyslipidemia

5.1 Parenteral Nutrition

Total parenteral nutrition (TPN) may alter plasma lipids and it is therefore important to monitor plasma lipids, particularly in those patients who have a lipid abnormality. Most of the published data about TPN and lipid disorders come from early days of TPN when Intralipid 10 % was used (24). This fat emulsion caused an increase of lipoprotein X (25). Twenty and 30 % percent long-chain triglyceride emulsions have much lower effect on lipoprotein X. A major difference is the phospholipid-to-triglyceride ratio that plays a role in the clearance differences among various emulsions. It has been suggested that large amounts of phospholipid caused the appearance of the
abnormal lipoprotein X in the blood of patients who received the 10% emulsion. There are fewer published data on the effect of the newer intravenous fat emulsions on plasma lipids, but the general consensus is that they alter lipid metabolism to a much lower degree. Other factors to be considered in the etiology of hypertriglyceridemia are glucose overload, sepsis, multiorgan failure, obesity, diabetes, liver disease, and renal failure, history of hyperlipidemia, pancreatitis, and medications such as propofol, cyclosporine, sirolimus and corticosteroids (26).

A multicenter Spanish study evaluated the prevalence of hypertriglyceridemia in acute care patients receiving TPN (27). The study included 260 patients from 14 hospitals. Lipid administration was 0.83 ± 0.37 g/kg/day. In this sample 68 patients (26.2%) showed hypertriglyceridemia. The authors carried out multiple logistic regressions to determine the clinical factors associated with PN hypertriglyceridemia. In the final analysis, the variables associated with a risk of developing hypertriglyceridemia included renal failure (OR, 10.56; adjusted b-coefficient for a dichotomous variable, 1.70), serum glucose (OR, 2.63; b-coefficient, 0.06), corticoid administration at doses over 0.5 mg/kg/day (OR, 7.98; b-coefficient, 0.97), pancreatitis (OR 4.381; b-coefficient, 0.64), and sepsis (OR, 4.48; b-coefficient, 0.24).

If hypertriglyceridemia occurs, the dextrose or lipid dosage should be reduced, depending on the cause. In comparison with cyclical infusion continuous lipid infusion over 24 hours facilitates lipid oxidation and improves plasma fatty acid profiles. The lipid infusion rate can be maintained at around 0.12 g/kg/hr, but lower rates may be necessary in critically ill patients or patients with impaired lipid clearance. When propofol is prescribed, the TPN lipid dosage should be adjusted to avoid hypertriglyceridemia. Therefore, the amount of lipids provided by the propofol dose should be subtracted from the intended lipid dose in the TPN formulation.

Patients receiving TPN may be monitored measuring baseline serum triglyceride concentrations before PN initiation with repeated measurement once the target lipid intake is reached. Other determinations such as serum phospholipids, fatty acids, cholesterol, and lipoprotein X levels are not performed routinely. Daily lipid infusion should be withheld when the serum is lipemic or when serum triglyceride concentrations exceed 400 mg/dL. To prevent essential fatty acid deficiency, 3-5% of total caloric intake should be as linoleic acid. Providing 300 mL of the 20% lipid emulsion twice weekly is sufficient to prevent essential fatty acid deficiency in adult patients.

One particular case of interest is the use of intravenous fat in acute pancreatitis. We have already mentioned that this condition can be caused by marked hypertriglyceridemia. The primary route of nutritional support in acute pancreatitis is enteral with parenteral nutrition being reserved for those patients unable to tolerate enteral feeding. One report of TPN causing hyperlipidemia and acute pancreatitis has been described, appearing to justify concern regarding TPN lipids in these patients (28). However, this is very uncommon. The management of this condition includes temporary omission of fat in the TPN prescription, or administration of moderate amounts of glucose and fat, along with insulin if necessary. Neither approach has been associated with adverse events, such as fatty acid deficiency or worsening of hypertriglyceridemia (29).

5.2 Enteral nutrition

Enteral feeds are formulated using an ideal mixture of fatty acids, with a careful selection and distribution of saturated, mono-unsaturated and poly-unsaturated fatty acids. Therefore, any effects on lipid metabolism are likely to be favourable, with clear advantages over ad libitum diets based on conventional food chosen by the individuals concerned.

However, there has been a case report of carnitine deficiency associated with long term enteral nutrition (30). The patient had a myopathy causing dysphagia and necessitating the use of enteral nutrition. Given the absence of other similar reports, it could be hypothesized that this patient may have had a primary metabolic disorder, decreasing the availability of carnitine, which was worsened by the administration of a diet free of carnitine.

6. Summary
The term dyslipidemia includes a number of abnormalities in plasma lipids, including an increase in total cholesterol, cholesterol transported by low density lipoprotein (cLDL) and triglycerides, and a decrease of cholesterol transported by high density lipoprotein (cHDL). Hyperlipidemia may be divided into primary, due to genetic factors, and secondary, due to acquired conditions such as diabetes. Elevated plasma lipids can accumulate in certain tissues. In the skin, xanthelasma and several types of xanthoma may develop. High levels of triglycerides may trigger acute pancreatitis. However, atherosclerosis is the most important clinical consequence of dyslipidemia. The development of the atherosclerotic plaque has been extensively studied and the main steps are briefly described. Clinical guidelines recommend lipid screening for primary prevention of coronary heart disease starting in adults at 20 to 45 years depending on the particular guideline. Lipid plasma concentrations are stratified according to the presence of different risk cardiovascular risk factors in an individual and could be different among different subjects. Therefore, recommendations on when to start medical therapy depend on LDL levels and on other risk factors for CHD as well.

Total parenteral nutrition (TPN) may alter plasma lipids and it is therefore important to monitor plasma lipids, particularly in those patients who have a lipid abnormality. The phospholipid-to-triglyceride ratio of the intravenous fat emulsion has been shown to have an influence on lipid metabolism. Other involved factors in this disorder are glucose overload, sepsis, multiorgan failure, obesity, diabetes, liver disease, renal failure, and antecedents of hyperlipidemia or pancreatitis, and certain medications. If hypertriglyceridemia occurs, the dextrose and/or lipid dosage may need to be reduced. When the serum is lipemic or when serum triglyceride concentrations exceed 400 mg/dL, it may be necessary to withhold daily lipid infusion. However, adequate amounts of IV lipids should be provided to prevent essential fatty acid deficiency.

References


