# DYSLIPIDEMIAS

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Dyslipidemias has a wide spectrum of clinical presentations : of these Coronary Heart Disease (CHD) is the leading cause of death in the developed world. However in many other places where affluence is increasing, there is rising incidence of CHD. In the past, this risk was evaluated on the basis of total cholesterol alone. Now there is a growing evidence that the risk of CHD is mediated through low density lipoprotein (LDL). High density lipoprotein (HDL) is considered as anti-atherogenic and a high level of HDL is a negative risk factor. There are new factors, which add to the complexity of the subject : mainly apolipoprotein particle size, oxidized forms of low density lipoprotein, atherogenic nature of triglycerides and lipoprotein (a).

**Lipoprotein Metabolism**

Lipoproteins are spherical complexes with a core of insoluble lipids surrounded be phospholipids and proteins which have both hydrophilic properties. The major function of lipoproteins is to transport the blood lipids. These lipoproteins are chylomicrons, very low density lipoproteins (VLDL), and high density liporproteins.

**Exogenous Lipid Pathway**

Lipid esters are hydrolyzed by digestive enzymes : free cholesterol, fatty acids, monoglyceride and diglyceride are released and absorbed in the duodenum (1). Within the enterocyte, large triglyceride rich chylomicrons consist mostly of triglycerides, small component of cholesterol ester, phospolipid and apolipoproteins (apo) A-I, B48, CI, CII, & CIII(1).

Chylomicrons are secreted into lymph ; they reach the systemic circulation via the thoracic duct and acquire more apolipoproteins (apo CII, apo CIII apo E), (2). Lipoprotein lipase (LPL), located primarily on the surface of the endothelial cells of capillaries of adipose tissue and muscle, hydrolyzes chylomicron triglycerides releasing free fatty acids, monoglyceride and diglyceride(3). Some phospholipids and apoprotein particles are transferred to HDL and chylomicron remnant particles are produced. The remnant particle contains cholesterol ester, apo B-48 and apo E. Hepatic cells have receptors which bind the remnant apo E. This results in the uptake and metabolism of the remnants by the liver (3).

**Endogenous Lipid Pathway**

The liver synthesizes triglycerides from glycerol and fatty acids. Cholesterol is derived from chylomicron remnants or synthesized through 3-hydroxy-3-methyl glutary coenzyme A reductase (HMG CoA). Triglycerides and cholesterol are incorporated into VLDL which is the major triglyceride containing lipoprotein in plasma of a fasting subject (1). VLDL contains mainly apo-B100 (4). This is a higher molecular weight protein than that of the gut B-48 (5). In addition to the apo B, there are few molecules of apo C and apo E.

VLDL particles are hydrolyzed by LPL. Apo C II is the activator of LPL. VLDL particles are transferred to LDL through intermediate density lipoprotein (IDL). Some of the IDL is taken up by the liver cells via LDL receptors (B&E) and not converted to LDL.

**Low Density Lipoprotein metabolism (LDL)**

LDL particles are derived from the catabolism of VLDL. They contain mostly cholesterol esters in the core and apo B-100 at the surface. They are taken up by the cells as the particles are recognized by specific receptors for apo B-100 (6) ; then the LDL particles are taken up by lysozome where cholesterol ester is converted to free cholesterol for cellular needs. LDL can also be taken up by non-receptor, nonsaturable and low affinity process. This is not regulated and may lead to accumulation of cholesterol ester (7). It has been estimated that normally about two thirds of LDL is degraded by high affinity receptor pathway with the remainder removed by nonreceptor mediated pathway(8).

**Reverse Cholesterol transport pathway**

HDL is synthesized in the liver and the intestine. It has a major role in transporting cholesterol from peripheral tissues to the liver. There is an interaction of HDL with putative HDL receptor to remove from the cell primary unesterified cholesterol. YyThe esterification of cholesterol in HDL by lecithin : cholesterol acyltransferase (LCAT), blocks the uptake of cholesterol is transported to the liver by one of three pathways ;

1 - transfer to LDL which is taken by the liver cells,
2 - selective uptake of cholesterol from HDL by liver cells and
3 - HDL is taken by the liver through apo E receptors (5).

**Apolipoproteins :**

**Apolipoprotein B :**

Apo B-100 is the major apoprotein of VLDL and LDL. It is synthesized in the liver. It is essential for VLDL structure, secretion from the liver and recognition of LDL by hepatic and extra hepatic receptors of LDL. Apo B-48 is produced by intestinal cells. It is essential for the assembly and secretion of chylomicrons(5).

**Apolipoprotein A-I :**

It is synthesized in the liver and small intestine. It is the main protein in HDL and is important for its maintenance. It is an activator of LCAT(3).

**Apolipoprotein A-II :**

Apo A is found mainly in HDL and chymicrons it is synthesized in the liver and small intestine. It's function is not yet well known (3).

**Apolipoprotein A-IV :**

Associated with chylomicrons HDL and VLDL. Main site of synthesis is small intestine. It is an activator of LACT (3).

**Apolipoproteins CI , CII and CIII :**

These are three proteins, all synthesized in the liver, and present in all major lipoproteins. The main function of apo CI is not yet known. Apo CII is an activator of LPL, while apo CIII may function as an inhibitor of LPL (3).

**Apolipoprotein E :**

This is synthesized primarily by the liver (9) and the brain but also by other tissues (10) and is present in nearly all the major lipoproteins. There are three major alleles for apo E gene (E2, E3, E4) and they vary in their affinity to LDL receptor. Homozygous for apo E2 may develop type III hyperlipidemia (4).

Lipoprotein (a) :

It was first identified by Berg (11). It consists of apolipoprotein (a) molecule linked by disulfide bridge to apolipoprotein B - 100 in lipid-rich LDL-like core (12) (13). Apo (a) has enormous molecular weight heterogeneity(14). It is well recognized that there is an association between lipoprotein (a) and CHD (14). However, how strong a risk factor is lipoprotein (a), remains controversial (14).

**Enzymes :**

**Lipoprotein lipase (LPL) :**

It is present in endothelial cells of adipose tissues, lung and skeletal muscles. It is stimulated by insulin and activated by apo CII. Its main function is the hydrolysis of the triglycerides of chylomicrons and VLDL thus producing chylomicron remnant and IDL.

Defective LPL activity may lead to severe hypertriglyceridemia in the homozygous and mild to moderate hypertriglyceridemia in the heterozygous.

**Lecithin :**

**cholesterol acyltransferase (LCAT) :**

It is synthesized in the liver and mediates transfer of fatty acids from lecithin to unesterified cholesterol in plasma. Apo A-I is a factor for LCAT esterification of free cholesterol (3).

Apo E plays a role in the disposition of VLDL. Some of the circulating VLDL remnants are removed directly by the liver in a process medicated by apo E (6).

**Cholesteryl ester transfer protein :**

It is found mostly in HDL. It exchanges cholesterol ester from HDL with triglycerides in chylomicrons or VLDL.

**Laboratory Measurements of Lipid and Lipoprotein :**

It is essential that for diagnosis of lipid disorders an accurate determination of lipid and lipoprotein concentration is performed.

There are analytical and preanalytical factors which are important and should be controlled. Preanalytical variations can be classified as biological, behavioral, clinical and dependent on specimen

collection (7).

There are recommendations from National Cholesterol Educational Program, Laboratory Standardization Panel, to minimize the effect of preanalytical factors on lipid and lipoprotein determinations.

The Panel recommended the following :

1 - An individual's lipid and lipoprotein profile should only be measured when the individual is in a metabolic steady state.

2 - Subjects should maintain their usual diet and weight for at least 2 weeks prior to the determination of their lipids or lipoproteins.

3 - Multiple measurement within 2 months, at least 1 week apart, should be performed before making a medical decision about further action.

4 - Patients should not perform vigorous physical activity within the 24-h period prior to testing.

5 -Fasting or non-fasting specimens can be used for total cholesterol testing.

However, a 12-h fasting specimen is required for triglyceridesand lipoprotein.

6 -The patient should be seated for at least 5 min before specimen collection.

7 -The tourniquet should not be kept on more than 1 min during venipuncture.

8 - Total cholesterol triglyceride, and HDL-C concentration can be determined in either serum or plasma. When EDTA is used as the anticoagulant, plasma should be immediately cooled to 2-4 c to prevent change composition and values should be multiplied by 1.03.

9 -For total cholesterol testing, serum can be transported either at 4 C or frozen. Storage of specimen at-20C is adequate for total cholesterol measurement. However, specimen must be stored frozen at-70 C or lower for triglyceride and lipoprotein and apolipoprotein testing.

10 -Blood specimens should always be considered potentially infectious and therefore must be handled accordingly.

## Xanthomas :

Xanthomas are a common presentation of disorder of lipid metabolism. It is important to recognize various forms of xanthomas since the dermatologist is often the first physician to be consulted.

Xanthomas are infiltrations of the skin varying from yellow to brown or red-purple in colour (15). Histologically, they are composed of lipid laden histiocytes, fibroblasts macrophages and Touton giant-cell.

### Clinical form of xanthomas :

**1 - Xanthelasma Palpebrarum :**

These are usually bilateral, symmetrical, soft yellow-orange, papules and plaques on the eyelids. The upper eyelid and the region around the inner canthus are most commonly involved (16). They may or may not be associated with hyperliporoteinemia.

**2 - Tendinous xanthomas :**

These are subcutaneous firm nodules attached to tendons, ligaments, fascia and periosteum (16). The overlying skin appears normal and moves freely.

Sites of predilection include : extensor tendons of the hands, knees, elbows and achilles tendons. They are found in severe hypercholesterolaemia and elevated levels of LDL as well as secondary hyperlipidaemias associated with prolonged cholestasis.

**3 - Tuberous zanthomas :**

Tuberous xanthomas vary in size and shape from small papules 0.5cm to lobulated firm nodules 2.5 cm or more (16). They appear as yellow to red in colour with predilection for extensor surfaces of the body e.g. elbows, knees, knuckles, buttocks and palms (17). They are seen in both primary and secondary hyperlipidaemias. (Fig 1,2,3,4)

**4 - Eruptive xanthomas :**

These are small yellow papules with an erythematous halo around the base. They appear in crops most commonly on the buttocks, shoulders and extensor surfaces of the arms and legs. The oral mucosa and face are occasionally affected (16). They appear in the presence of high triglyceride levels in the plasma.

**5 - Plane xanthomas :**

Plane xanthomas can involve any site and appears as yellow or orange macules or slightly palpable plaques (16). When they involve the creases of palms and fingers, they are termed "xanthochromia striatum palmaris", and are associated with condi-

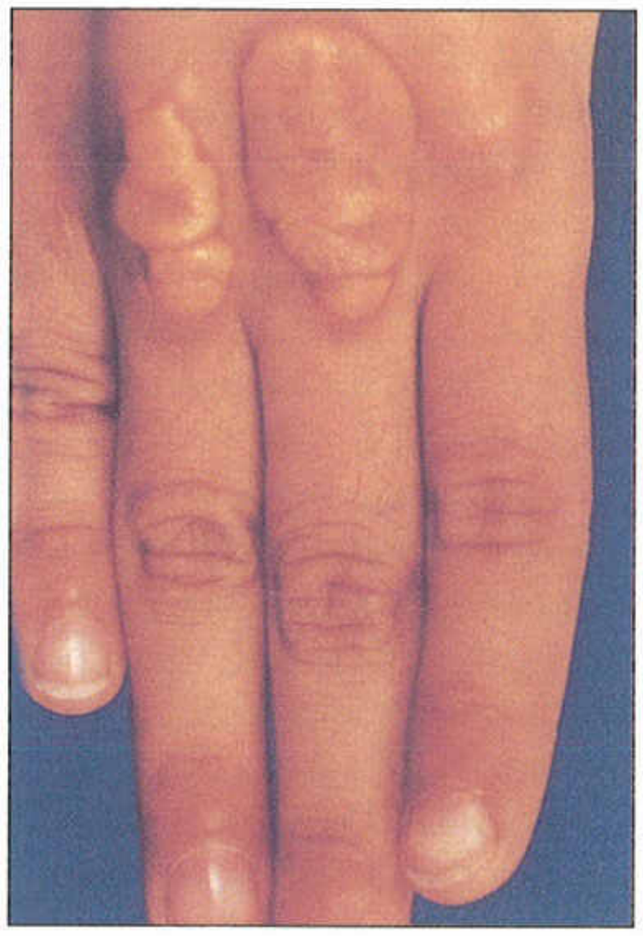
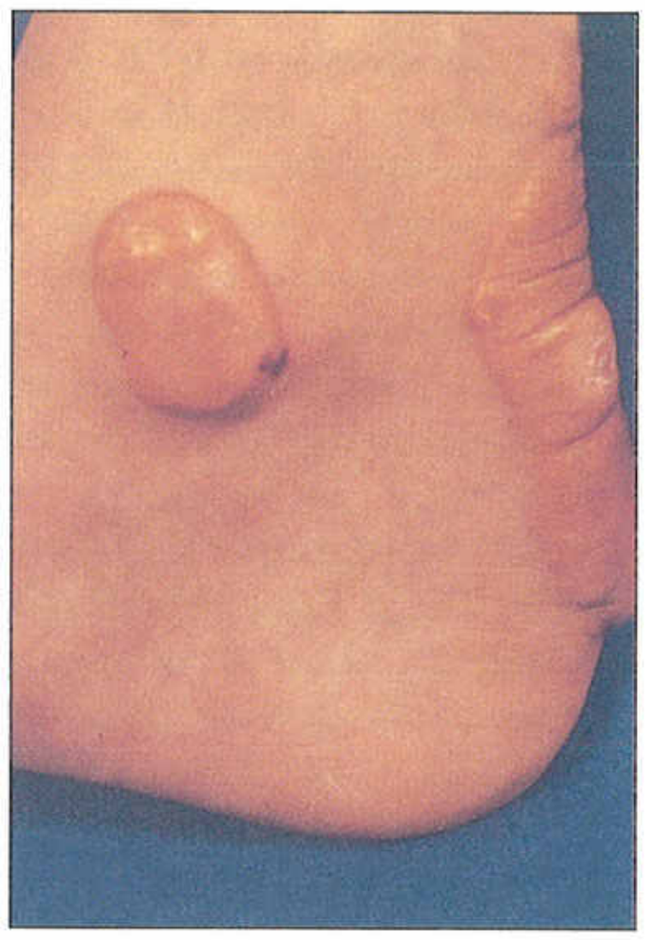


Figure 1



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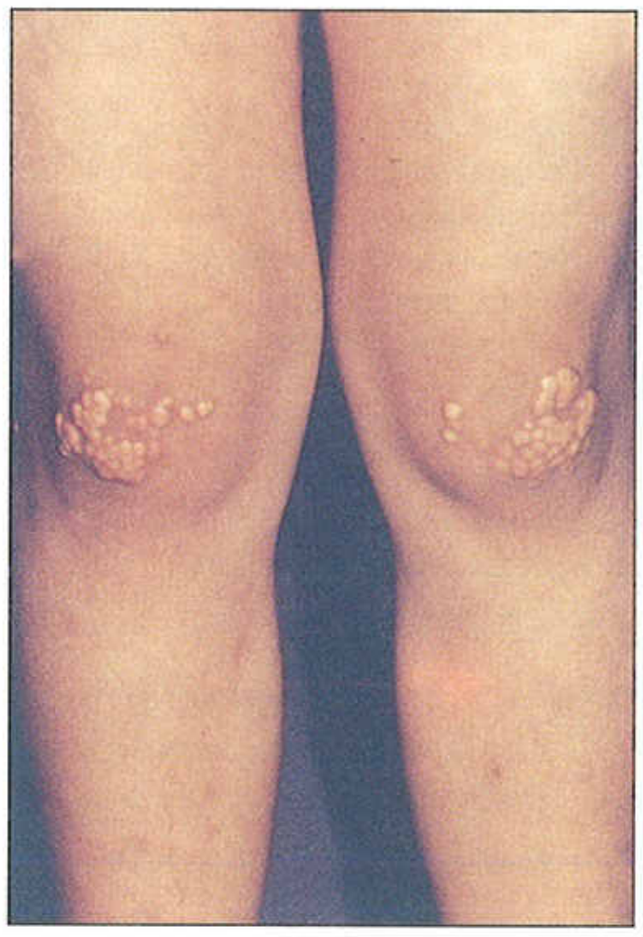

Figure 3

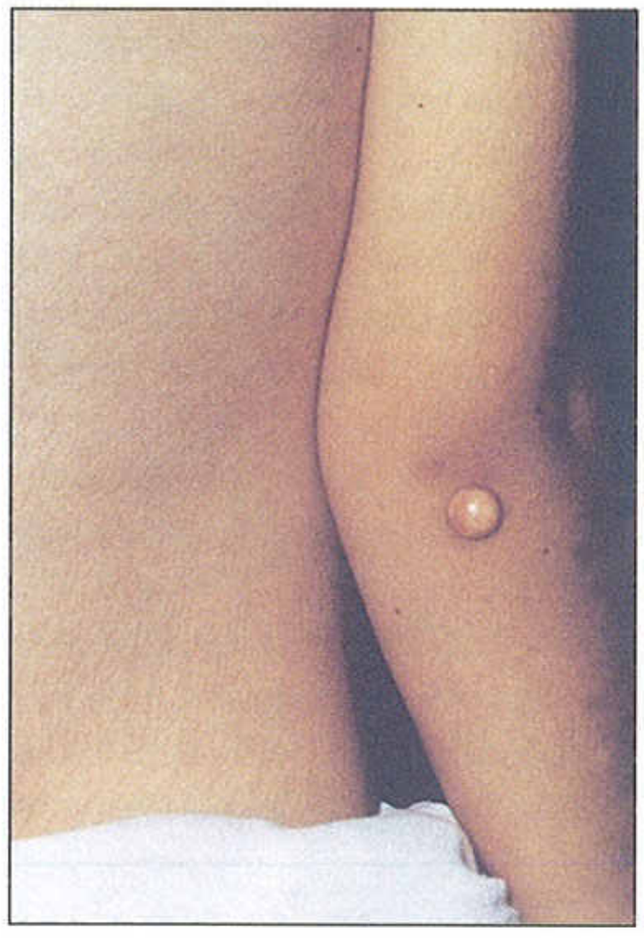

Figure 4

tions causing high plasma cholesterol and triglyceride levels (17).

A generalized plane anthoma with extensive yellow-orange lesions involving the face, neck and upper part of the trunk and arms is seen in association with various paraproteinemias.

**6 - Intertriginous xanthomas :**

These are xanthomas in the finger werbs and anal clefts (15).

## Disorders of lipoproteins :

Lipoprotein disorders are now classified according to the abnormalities of lipoproteins instead of the Fredrickson classification(18).

**Triglyceride-rich lipoprotein and hypertriglyceridemia :**

Severe hypertriglyceridemia greater than 11 mmol/L is almost caused by increased levels of chylomicrons. The latter give a milky appearance to both plasma and whole blood. Affected persons may have hepatosplenomegaly, eruptive xanthomas and lipemia retinalis (19).

A homozygous genetic deficiency in LPL leads to inability to catabolize dietary triglyceride (type 1). (20). Patients have recurrent pancreatitis but not increased risk of coronary artery disease (CAD). Heterozygous LPL deficiency causes increased postprandial and milder form of fasting hypertriglyceridemia. Milder hypertriglycerdemia (2.8 to 5.65 mmol/l) is asymptomatic and is caused by VLDL overproduction as occurs in hypertriglyceridemia (Type IV) or familial combined hyperlipidemia (elevated VLDL, LDL : Type II-B)> Renal failure, diabetes mellitus, alcohol, estrogens and severe obesity are associated with elevated VLDL.

**Cholesterol-rich lipoproteins and hypercholesterolemia :**

All lipoproteins contain cholesterol, hence a marked elevation of VLDL and chylomicrons will cause increased levels of blood cholesterol. Elevated LDL and less commonly HDL present as hypercholesterolemia without hypertriglyceridemia. In familial hypercholesterolemia (Type IIa), LDL levels are high. Heterozygous carriers present with LDL levels greater than 6 mmol/L, and often have a positive family history of CAD in

the third to fifth decade of life. Patients have tendon xanthomas best appreciated as diffuse or nodular thickenings of the achilles tendon. These are an age related phenomenon with 7% of heterozygotes exhibiting the condition below the age of 19 compared with 75% in the parents (21). Most cases are due to a defect of the LDL receptor. Three types are recognized :

1 - Type I : absent LDL receptor.
2 - Type II :LDL receptors are present but there is defective binding, and
3 -Type III :receptor are present but internaliza tion is defective (22).

Definitive diagnosis of familial hypercholesterolemia can be made using monoclonal anti LDL antibodies.

Elevated HDL levels may be protective for CAD. Low HDL levels are associated with increased risk for CAD.

**Elevated cholesterol and triglyceride concentrations :**

Elevations of both VLDL and LDL occur in familial combined hyperlipidemia (type II-b) documented first in 1973 by Goldstein et al (23). It may be the most common genetic disorder accounting for premature CAD.

Overproduction of hepatic apo B has been reported (24). Some patients may also be heterozygote for LPL deficiency. The phenotype of this disorder varies, and patients may present with elevated levels of LDL and/or VLDL.

A less common cause of combined increase in blood triglycerides and cholesterol is dysbetaliproteinemia (type III). This disorder is caused by elevated levels of remnant lipoproteins (IDL) due to abnormal forms of apo E. Signs of this disease include palmar xanthomas and tuberous xanthomas. Dysbetalipoproteinemia increases the risk for CAD and peripheral vascular disease (25).

**Secondary causes of Hyperlipoproteinemia :**

| These include : | | | | | |
|---|---|---|---|---|---|
| 1 - Hypothyroidism : (26) | ↑ | LDL | ↑ | IDL | |
| 2 - Diabetes Mellitus : | ↑ | VLDL | ↑ | HDL | |
| 3 - Renal failure : | ↑ | VLDL | ↑ | HDL | |
| 4 - Nephrotic syndrome : (27) | ↑ | LDL | ↑ | IDL | ↑ VLDL |
| 5 - Severe obstructive liver disease : (28) | ↑ | Cholesterol | | | |
| 6 - Drugs : | | | | | |
| - Thiazides | ↑ | LDL | | | |
| - B-blockers : | ↑ | HDL | | | |
| - Anabolic steroids : | ↑ | HDL | | | |
| - Phenytoin,phenobarbital, oral estrogen | ↑ | HDL | | | |

**Primary Hypoalphalipoprotinemia :**

This is a genetic disorder manifested by isolated low HDL cholesterol leading to premature CAD. The primary genetic defect is unknown.

**Treatment :**

The goals of treatment have been outlined by the National Cholesterol Program II which emphasizes lowering elevated LDL cholesterol as the primary target of therapy because studies have consistently shown that such a step reduces CAD incidence. Patients with high triglyceride levels (11 mmol/L) should receive pharmacotherapy to reduce the risk of pancreatitis. Patients with diabetes mellitus and hypertriglyceridemia should be treated because the latter is a risk factor for CAD in diabetics.

**Nonpharmacological therapy :**

1 - Low fat low cholesterol diet (see table I) : use step I diet for three months ; if desirable levels are

not achieved (table II) then move on to step II diet. If after six months of dietary treatment, desirable cholesterol levels are still not achieved, then institute drug-therapy.

2 - Weight loss

3 - Increased physical activity

4 - No cigarette smoking

In children, the goal is to provide adequate calories for development with general decrease in the amount of total and saturated fat in the diet.

**Pharmacological therapy :**

1 - Bile acid resins : these bind bile acids in the intestine preventing reabsorption in the terminal ileum. They lower LDL cholesterol but increase triglycerides.

Advantages : safe and effective.

Disadvantages : unpleasant side effects of bloating, nausea and constipation ; they can bind to other medications.

2 - Nicotinic acid : it effectively lowers VLDL and LDL levels. It inhibits secretion of VLDL from the liver and thereby lowers LDL. It raises HDL significantly.

Advantages : safe, effective and cheap.

Disadvantages : flushing, glucose intolerance and elevation of liver enzymes especially with the slow release forms. Unfortunately, very few patients can put up with its unpleasant side effects.

3 - HMG CoA-reducatase inhibitors : or statins lower LDL cholesterol by competitively inhibiting the rate-limiting enzyme for cholesterol biosynthesis HMG CoA-reductase. They increase LDL receptor activity in the liver.

Advantages : very effective in lowering LDL ; effective in reducing CAD in angiographic (regression) trial.

Disadvantages : long term safety not established ; moysitis, liver function tests abnormalities. The following drugs must not be combined with the statins because of increased risk of myositis : cyclosporin, gemfibrizol, nicotinic acid and erythromycin.

4 - Fibric acid drivatives : mostly effective in reducing VLDL levels. They also raise HDL. Do not use in renal insufficiency.

5 - Probucol : is moderately effective in reducing LDL but it also decreases HDL : this has limited its use in the treatment of hyperlipidemia. Its antioxidant properties prevent lipid peroxidation and hence inhibit LDL uptake by macrophages thus reducing atherogenesis in experimental animals (29).

In children, drug therapy is usually reserved for those than 10 years, who failed dietary therapy over 6- months period. The National Cholesterol Education Program (NCEP) pediatric panel suggests drug treatment for the following :

1 - LDL 5 mmol/L

2 - LDL 4.3 mmol/L and family history of premature heart disease or the presence of other risk factors. The current drugs recommended are the bile acid resins.

***Table 1***

| NUTRIENT | STEP 1 | STEP 2 |
|---|---|---|
| Calories | Adequate to promote normal growth and development | Same |
| Total fat | < 30% of calories | Same |
| Saturated fat | < 10% of calories | <7% of calories |
| Polyunsaturated fat | Up to 10% of calories | Same |
| Monounsaturated fat | Remaining fat calories | Same |
| Cholesterol | <300 mg/day | <200 mg/day |
| Carbohydrates | Approximately 55% of calories | Same |
| Protein | About 15% to 20% of calories | Same |

National Cholesterol Education Program

***Table II***

**LDL Cholesterol Treatment Guidelines**

| | Level to begin therapy | | |
|---|---|---|---|
| | Diet therapy | Drug therapy | Therapeutic |
| | (mmol/L) | (mmol/L) | Goals(mmol/L) |
| Fewer than 2 risk factors | >4.1 | > 4.9 | < 4.1 |
| Two or more risk factors | >3.3 | > 4.1 | < 3.3 |
| With CHD | >2.6 | >3.4 | < 2.6 |

National Cholesterol Program Cut points for LDL Cholesterol

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