**Dyslipidemias**

***Definition:***

* Dyslipidemias(**one or more abnormalities of blood lipids**) produce **atherosclerosis**, which in turn produces coronary artery disease (CAD).
* Successful management of dyslipidemias alters the natural course of atherosclerosis and prevents CHD as well as other forms of atherosclerosis.

***Lipid Metabolism and Drug Effects***

* The journey begins with how lipids are **formed,** **transported**, and **utilized**;. At the center of these processes are **cholesterol,** **triglycerides (TG**), and **phospholipids**.
* **cholesterol** plays the central role in the pathogenesis of **atherosclerosis..** It is the precursor molecule for the **formation of bile acids**, the **synthesis of steroid hormones**, and the **formation of cell membranes**.
* **TG** are an important source of **stored energy** in adipose tissue.
* **Phospholipids** are essential for cellular function and the transport of lipids in the circulation by forming a membrane bilayer of lipoproteins .

***Types & Etiology of dyslipidemia***

1. **Primary dyslipidemia**

**The primary hypercholesterolemia**– ***increase in LDL-C***

 Familial Hypercholesterolemia FH

Familial defective apoB-100

**The primary mixed ( combined ) hyperlipidemias**- ***increase LDL-C and TG***

 Familial combined hyperlipidemia FCHL

Familial hyperapobetalipoproteinemia

* *Patients with FCHL commonly are overweight and hypertensive and also may have diabetes or hyperuricemia.*

**The primary Hypertriglyceridemia**-***increase in TG***

Familial lipoprotein lipase deficiency,

Familial apo C11 deficiency.

Familial Dysbetalipoproteinemia (type III hyperlipidemia),

* *individuals with an apolipoprotein E2:E2 phenotype have delayed clearance of VLDL remnant (and possibly chylomicron) and a reduced conversion of IDL to LDL particles.*

**Hypo-alpha-lipoproteinemia *Low HDL-C <40 mg/dL***

* Hypoalphalipoproteinemia) has been linked to a defect in the ABCA-1 transporter responsible for the efflux of cholesterol from peripheral cells.
* **Tangier disease**, which is characterized by low HDL-C, orange tonsils, and hepatosplenomegaly,
1. **Secondary dyslipidemia** – ***moderate TG elevation /moderately high LDL-C a***

 ***low HDL-C level (<40 mg/dL***

* Atherogenic Dyslipidemia
* Most commonly, overweight or obese with increased waist circumference, hypertensive, and insulin resistant with or without diabetes and are said to have the metabolic syndrome.
* Causes Disease or Drugs

**Box 24.1 Examples of disorders known to adversely affect the lipid profile**

Anorexia nervosa

Bulimia

Type 1 diabetes

Type 2 diabetes

Hypothyroidism

Pregnancy

Inappropriate diet

Alcohol abuse

Chronic renal failure

Nephrotic syndrome

Renal transplantation

Cardiac transplantation

Hepatocellular disease

Cholestasis

Myeloma

1. **Polygenic Hypercholesterolemia –** ***increase LDL-C***
* Environmental ( e.g., poor nutrition, sedentary lifestyle)and genetic factors
* Saturated fatty acids in the diet of these patients can reduce LDL receptor activity, thus reducing the clearance of LDL particles from the systemic circulation.
* Family history of premature CHD is present in approximately 20% of cases.

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| **Characteristics of Common Lipid Disorders** |
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| ***Disorder*** | ***Metabolic Defect*** | ***Lipid Effect*** | ***Main Lipid Parameter*** | ***Diagnostic Features*** |
| **Polygenic hypercholesterolemia** | ↓LDL clearance | ↑LDL-C | LDL-C: 130–250 mg/dLTG: 150–500 mg/dL | None distinctive |
| **Atherogenic dyslipidemia** | ↑VLDL secretion,↑C-III synthesis   ↓LPL activity   ↓VLDL removal | ↑TG↑Remnant VLDL↓HDL↑Small, dense LDL | HDL-C: <40 mg/dL | Frequently accompanied by central obesity or diabetes |
| **Familial hypercholesterolemia (heterozygous)** | Dysfunctional or absent LDL receptors | ↑LDL-C | LDL-C: 250–450 mg/dL | Family history of CHD, tendon xanthomas |
| **Familial defective apoB-100** | Defective ApoB on LDL and VLDL | ↑LDL-C | LDL-C: 250–450 mg/dL | Family history of CHD, tendon xanthomas |
| **Dys beta lipoproteinemia** **(type III hyperlipidemia**) | ApoE2:E2 phenotype, ↓VLDL remnant clearance | ↑Remnant VLDL, ↑IDL | LDL-C: 300–600 mg/dLTGs: 400–800 mg/dL | Palmar xanthomas, tuberoeruptive xanthomas **.**Triggered by other metabolic problems |
| **Familial combined hyperlipidemia** | ↑ApoB and VLDL production | ↑CH, TG, or both | LDL-C: 250–350 mg/dLTGs: 200–800 mg/dL | Family history, CHDFamily history, Hyperlipidemia |
| **Familial hyper apo beta lipoproteinemia** | ↑ApoB production | ↑ApoB | ApoB: >125 mg/dL | None distinctive |
| **Hypo alpha lipoproteinemia** | ↑HDL catabolism | ↓HDL-C | HDL-C: <40 mg/dL | None distinctive |

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**Clinical Assessment**

* As a routine, every new patient with hypercholesterolemia should be evaluated for four things in the following order:
1. Secondary causes - Disease or Drugs

High cholesterol level, *include diabetes mellitus, hypothyroidism, nephrotic syndrome, and obstructive liver disease. Selected drugs* -Hypertriglyceridemia *include chronic renal failure; diabetes mellitus; alcohol use and abuse; a sedentary lifestyle; obesity; and the use of TG-raising drugs, including β-blockers, estrogens, and glucocorticoids.*

 (2) Primary familial disorders,

 (3) Presence of CHD

 (4) Positive Risk Factors for CHD

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| **Positive Risk Factors (↑Risk)** |
| Age: Male ≥45 yr Female: ≥55 yrFamily history of a premature CHD (definite MI or sudden death before 55 yr in father or other male first-degree relative or before 65 yr in mother or other female first-degree relative)Current cigarette smokingHypertension (≥140/90 mm Hg or on antihypertensive drugs)Low HDL-C (<40 mg/dL) |
| Negative Risk Factor (↓Risk, protective) |
| High HDL-C (≥60 mg/dL) |
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* ***All adults from the age of 40 years***, with **no history** of CVD or diabetes, and not receiving treatment for raised blood pressure or dyslipidaemia, should ***receive opportunistic screening every 5 years in*** primary care.
* Those with a ***cardiovascular risk >20% over 10 years*** are deemed to require **treatment** according to current national and international guidelines,
* ***Risk assessment is not required when the individual is 75 years of age*** or older, or they have pre-existing CVD. These individuals are already assumed to have a 10-year risk of at least 20%.

**Diabetes mellitus**

**Type 1 diabetes.**

* In patients with type 1 diabetes, **HDL-C may appear high but for reasons** which are unclear, it does not impart the same degree of protection against CVD as in those without diabetes. It is, therefore, not appropriate to use cardiovascular risk prediction charts that utilise the TC:HDL-C ratio in patients with type 1 diabetes.
* Patients with type 1 diabetes **have a two- to three-fold increased risk** of developing CVD.

**Type 2 diabetes.**

* Patients with type 2 diabetes typically **have increased triglycerides and decreased HDL-C.**
* Levels of TC may be similar to those found in non-diabetic individuals but the
* patient with type 2 diabetes often has increased levels of **highly atherogenic small dense LDL particle**s.
* Individuals with type 2 diabetes and **aged over 40 years**, but without CVD, are often considered to have the ***same cardiovascular risk as patients without*** diabetes who have survived a myocardial infarction.
* This assumption is generally appropriate but influenced by **patient age**, **duration of diabetes** and **gender** and holds better for women than men.
* In some guidelines, the criteria for at risk is age above 40 years but with one other risk factor present, for example, **hypertension, obesity, smoker**, etc.

National Institute of Health and Clinical Excellence (2008a)

***consider an individual with type 2 diabetes to be at high premature cardiovascular risk for their age unless he or she:***

• is not overweight

• is normotensive (<140/80 mmHg in the absence of antihypertensive therapy)

• does not have microalbuminuria

• does not smoke

• does not have a high-risk lipid profile

• has no history of CVD and

• has no family history of CVD.

* Where the individual is found to be at risk the patient is typically started on 40 mg simvastatin , the dose can be titrated up to **simvastatin 80 mg a day** if lipid levels are not reduced to less than 4 mmol/L for TC and less than 2 mmol/L for LDL-C on 40 mg simvastatin.
* In those who do not reach target, **80 mg atorvastatin** may be tried.

**Primary prevention**

* ***All adults from the age of 40 years***, with **no history** of CVD or diabetes, and not receiving treatment for raised blood pressure or dyslipidaemia, should ***receive opportunistic screening every 5 years in*** primary care.
* Those with a ***cardiovascular risk >20% over 10 years*** are deemed to require **treatment** according to current national and international guidelines,
* ***Risk assessment is not required when the individual is 75 years of age*** or older, or they have pre-existing CVD. These individuals are already assumed to have a 10-year risk of at least 20%.
* When using the risk prediction charts a number of factors **need to be taken** into account at screening and include:

• ***Age****:* in individuals under 40 years of age the charts overestimate risk; over the age of 70 years risk is underestimated by the charts and most have a 10-year risk >20%.

• ***Gender****:* there are separate charts for men and women.

• ***Ethnicity****:* the risk prediction charts have only been validated in white caucasians and underestimate risk in individuals from the Indian subcontinent (India, Pakistan, Bangladesh and Sri Lanka) by a factor of 1.5.

• ***Smoking history****:* individuals who have stopped smoking within 5 years of assessment should be considered as current smokers.

• ***Family history****:* risk increases by a factor of 1.5 when CHD has occurred in a first-degree relative (parent,offspring, sibling) male <55 years or female <65 years, when a number of family members have developed CHD risk increases by a factor of 2

• ***Body mass index* (*BMI*) *and waist circumference****:* the charts do not adjust for either BMI or waist circumference; these factors need to be taken into account in the clinical decision-making process.

• ***Non-fasting blood glucose****:* if non-fasting glucose >6.1 mmol/L, the individual should be assessed for impaired glucose regulation or diabetes. I

ndividuals with type 2 diabetes aged over 40 years and with an additional cardiovascular risk factor are considered to be at greater than 20% risk over 10 years and eligible for treatment.

 In those who are 40 years of age or older but without any additional risk factor, a specific risk engine is available.

**Treatment with Primary prevention**

* lifestyle advice address management of dyslipidaemia,
* optimize use of antihypertensive agents, other cardiovascular protective therapies and achieve tight blood glucose control as appropriate.
* In patients without evidence of arterial disease, treatment must be considered if the risk of CVD is *>*20% or more over 10 years

**Diet Therapy** Principles to teach include the following:

* Eat less high-fat food (especially food high in saturated fats).
* Replace saturated fats with monounsaturated fats and fish oils whenever possible.
* Eat less high-cholesterol food.
* Choose foods high in complex carbohydrates (starch and fiber).
* Attain and maintain an acceptable weight.

**Lifestyle Changes**

* Weight reduction in the overweight patient can reduce LDL-C
* Smoking cessation substantially reduces the risk of CHD, pulmonary disease, and cancer
* Increasing physical activity should be a component of the treatment of any patient with high blood cholesterol. Regular physical exercise may reduce TG and VLDL-C levels, raise HDL-C levels slightly, promote weight loss or maintenance of desired weight, lower BP, and cause favorable changes in coronary blood flow.

**Treatment will normally include**:

• *A lipid-lowering agent* such as simvastatin 40 mg/day (or alternative) but no treatment targets are set

• *personalised information on modifiable risk factors* including physical activity, diet, alcohol intake, weight and tight control of diabetes

• *advice to stop smoking*

• advice and treatment to *achieve blood pressure below 140 mmHg systolic and 90 mmHg diastolic.*

**Secondary prevention**

* ***Patients with CVD and levels of TC >4 mmol/L and LDL-C >2 mmol/L*** are the ones most likely to benefit from treatment with lipid-lowering agents.
* Typical of individuals who fall into this category are patients with a history of *angina, myocardial infarction, acute coronary syndrome, coronary artery bypass grafting, coronary angioplasty or cardiac transplantation as well as patients with evidence of atherosclerotic disease in other vascular beds such as patients post-stroke or TIA, and those with peripheral arterial disease*.
* As in the situation with primary prevention outlined above, if an individual is to receive a lipid-lowering agent as part of a secondary prevention strategy, the possibility of a familial dyslipidaemia and the need to assess .

**Treatment with Secondary prevention**

In individuals diagnosed with CVD or other occlusive arterial disease, treatment should include:

• *a lipid-lowering agent* to lower TC aiming towards a TC <4 mmol/L and LDL-C <2

 mmol/L

• *advice to stop smoking*

• *personalised information on modifiable risk* factors including physical activity, diet, alcohol intake, weight and diabetes

• *advice and treatment to achieve blood pressure at least below 140 mmHg systolic and 90 mmHg diastolic*

• *tight control of blood pressure and glucose* in those with diabetes

• ***low-dose aspirin*** *(75 mg daily)*

*•* ***ACE inhibitors***especially for those with left ventricular dysfunction, heart failure, diabetes, hypertension or nephropathy

• ***B-blocker*** for those who have had a *myocardial infarction* and in those with heart failure

• ***warfarin (or aspirin***) for those with *atrial fibrillation* and additional stroke risk factors.

**Drugs of Choice for Dyslipidemia**



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| ***Lipid Disorder*** | ***Drug of Choice*** | ***Alternative Agents*** | ***Combination Therapy*** |
| Polygenic hypercholesterolemia | Statin | Resin, ezetimibe, niacin Combination | Statin-ezetimibe, statin-resin, resin-niacin, statin-niacin |
| Familial hypercholesterolemia or severe polygenic hypercholesterolemia | Statin (high-dose) | – | Statin-ezetimibe, statin-resin, resin-niacin, statin-niacin, statin-ezetimibe-niacin, statin-resin-niacin |
| Atherogenic dyslipidemia | Statin, niacin, fibratea | Statin, niacin, fibratea | Statin-niacin, niacin-resin, niacin-fibrate |
| Isolated low HDL | Statin | Niacin | Statin-niacin |
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**Combination Drug Therapy**

Four drugs effectively reduce LDL-C: **a statin, a resin, ezetimibe, and niacin**

* **niacin and resin** result in LDL-C reductions of 32% to 43%;
* **statin and a resin** lower LDL-C by 45% to 55%,
* **ezetimibe plus a statin** reduces LDL-C by 46% to 70%.
* **statin plus resin plus niacin-three-drug regimen**, LDL-C reductions of 50% to 60%

 *The combination of a statin and ezetimibe is the one best tolerated and offers the most convenient once-a-day dosing of the possible combinations.*

**Lipid-lowering**  **Therapy**

***Bile Acid Resins***

* Resins are not absorbed from the gastrointestinal (GI) tract and thus lack systemic toxicity.
* **They reduce Total cholesterol and LDL cholesterol in a dose-dependent manner.**
* ***The mechanism of action*** with a resin that interferes with bile acid recycling can cause a substantial upregulation of LDL receptors and enhance removal of cholesterol from the blood.
* effectively lowers LDL-C when combining a drug that reduces hepatocellular cholesterol biosynthesis (e.g., statins)
* Therapy should be initiated with one packet, scoop, or tablet of resin daily**.**
* Because of numerous GI side effects and the unpleasant granular texture of the powder. A new bile acid resin, **Colesevelam** (WelChol), is available in 0.625-g tablets; the daily dose is six tablets (3.8 g) administered in one or two divided doses daily.

***Statins***

* Statins the most potent cholesterol-lowering potential is composed of the statins. also reduce TG levels and increase HDL-C modestly .
* ***The mechanism of action*** Statins competitively inhibit the enzyme responsible for converting HMG-CoA that reduces hepatocellular cholesterol biosynthesis
* The available statins are

**simvastatin atorvastatin**, **fluvastatin** **,lovastatin** **,pravastatin, rosuvastatin**),

**Rosuvastatin** provides the most substantial LDL-C lowering, followed by **atorvastatin, simvastatin, lovastatin, pravastatin, and fluvastatin in** descending order.

* The efficacy of many statins is greater if administered in the evening to *coincide with the nighttime upturn in endogenous cholesterol biosynthesis*;
* **atorvastatin, and rosuvastatin** with a longer half-life and more potent LDL-C lowering, may be *administered without regard to time of day*.

***Fibric Acid Derivatives***

* **Gemfibrozil** (Lopid) and **fenofibrate** (TriCor) **clofibrate** [Atromid S**])** lower TG levels in patients with hypertriglyceridemia, raise HDL-C
* In patients who have *TG levels >1,000 mg/dL and are at risk for developing pancreatitis, fibrates, + niacin, are the drugs of choice.*
* patients with familial dysbetalipoproteinemia and mixed hyperlipidemia, fibric acid derivatives are the drugs of choice.
* Persons most benefit are those with *diabetes or with the metabolic syndrome*.

***Cholesterol Absorption Inhibitors - Ezetimibe***

* Ezetimibe represents a class of lipid-altering drugs called cholesterol absorption inhibitors.
* ***The mechanism of action*** ability to reduce LDL-C by an action in the gut, with minimal systemic exposure (interferes with the active absorption of cholesterol from the intestinal lumen )
* This suggests that the drug may be very safe, much like the resins. It is administered once a day as a 10-mg tablet.

***Niacin***

* (**nicotinic acid**) is *a water-soluble B3 vitamin* that can improve the levels of all serum lipids.
* ***The mechanism of action*** Niacin inhibits the mobilization of free fatty acids from peripheral adipose tissue to the liver, reduced synthesis and secretion of VLDL particles by the liver**.**

*Niacin is also the only drug that lowers Lp(a), Reduction in LDL-C follows a linear relationship to dose:*

* **Crystalline niacin** should be started at a low level (e.g., 250 mg in two or three divided doses daily) and slowly titrated as tolerated (e.g., daily doses increased by 250 mg every 3 to 7 days) to a maximum of 3,000 mg/day **,**
* **Sustained-release** (timed-release) dosage forms of niacin were developed to reduce the flushing side effects associated with crystalline niacin.
* E**xtended-release** dosage form of niacin, Niaspan, is available by prescription to treat elevated cholesterol and TG levels and appears to be better tolerated than either the crystalline or sustained-release forms.

***Fish Oils***

* Fish oils predominantly contain polyunsaturated (omega-3) fatty acids, which lower TG levels significantly (30% to 60%) but have variable effects on cholesterol levels.

***Antioxidant Therapy***

* Only oxidized LDL is taken up by macrophage cells in the initial phase of atherogenesis.
* **Vitamins E, C, and beta-carotene** (the precursor of vitamin A) have antioxidant properties and have been variably recommended to prevent CHD.

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