Cardiology Lab Essentials
Chapter 4

LABS IN DYSLIPIDEMIA AND CARDIOVASCULAR DISEASE

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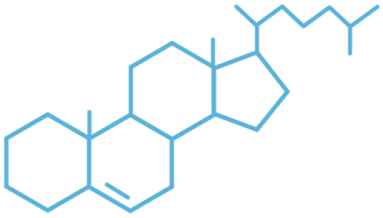
EXPLORING LIPOPROTEIN METABOLISM

Lipids are an essential component of the human body. They are important for generating and storing energy, forming hormones and vitamins, building cell membranes, and providing insulation to allow nerve conduction, or prevent heat loss.

The two most important lipids in cardiac labs



Cholesterol

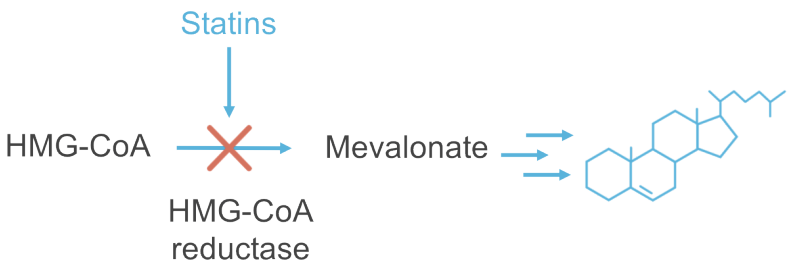
Triglycerides

Cholesterol

Cholesterol is used in the formation of steroid hormones such as sexual hormones, cortisol and aldosterone, the formation of vitamin D, and the production of bile. Cholesterol is also required to maintain cell membrane integrity.

There are two main sources of cholesterol. It can be absorbed from the intestinal lumen or synthesized by any cell in the human body through the degradation of amino acids, fatty acids or carbohydrates.

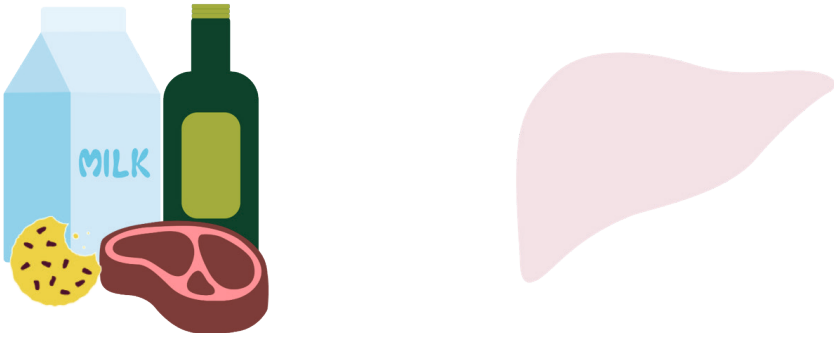
The rate limiting step in cholesterol production is the reduction of HMG-CoA to mevalonate by the enzyme HMG-CoA reductase. Statins, the most important agent in dyslipidemia treatment and cardiovascular prevention, are inhibitors of HMG-CoA reductase.



Triglycerides

Triglycerides are stored in adipose cells as large fat globules and are the major form of energy storage. They are composed of three fatty acid chains bound to a glycerol backbone. When these fatty acids are oxidized, energy is set free. In addition to acting as the body's energy stores, triglyceride-rich adipose tissue also provides insulation, preventing heat loss, and triglycerides in the intestines are important for aiding the absorption of the fat-soluble vitamins A, D, E, and K.

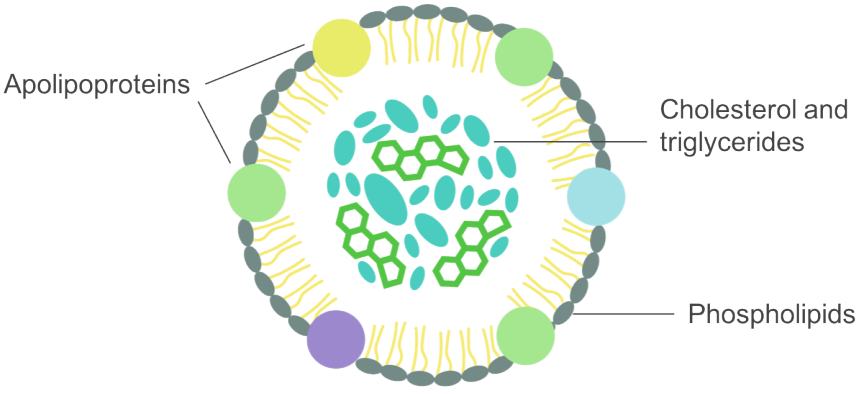
There are two main sources of triglycerides: diet and endogenous production by liver tissue.



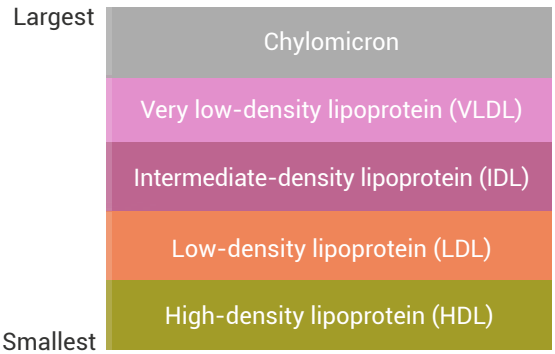
Lipoproteins

Since lipids are poorly soluble in water, they need to be attached to proteins in order to be transported in the blood. These transport proteins are called lipoproteins.

Lipoproteins are typically spherical complexes with a hydrophobic core containing cholesteryl ester and triglycerides, and a surface made up of free cholesterol and phospholipids. The surface also contains a variety of proteins, which are known as apolipoproteins. The apolipoproteins help to give structural integrity, activate enzymes involved in lipoprotein metabolism, or facilitate the uptake of lipoproteins into their target cells.



Different types of lipoproteins differ in their size, composition of cholesteryl ester and triglycerides, and in the combinations of apolipoproteins they express.

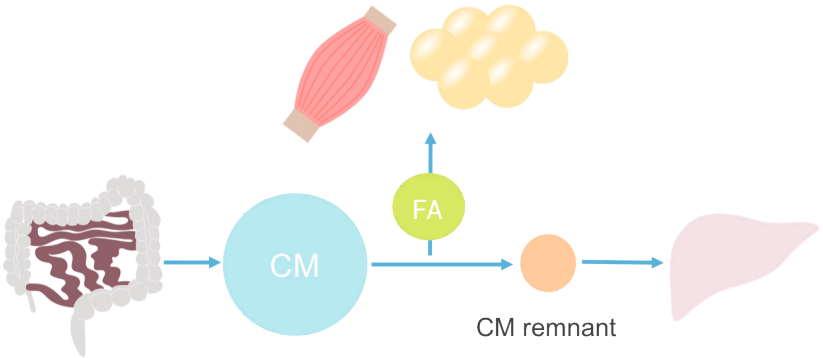


Chylomicrons and VLDL contain mainly triglycerides. With decreasing size, the share of core cholesterol increases.

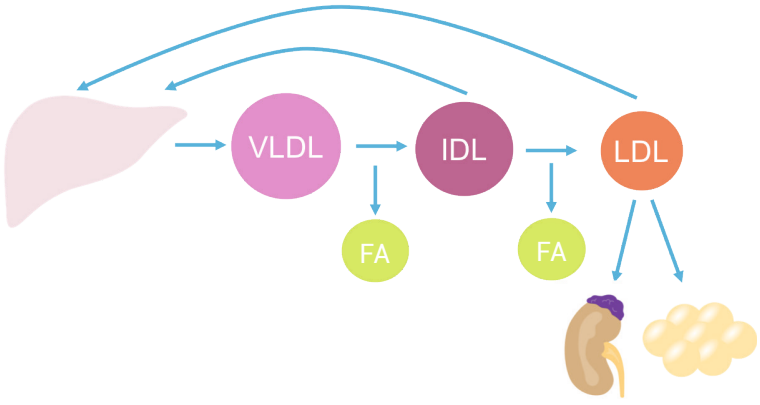
Lipid trafficking pathways

We can differentiate distinct trafficking pathways for cholesterol and triglycerides.

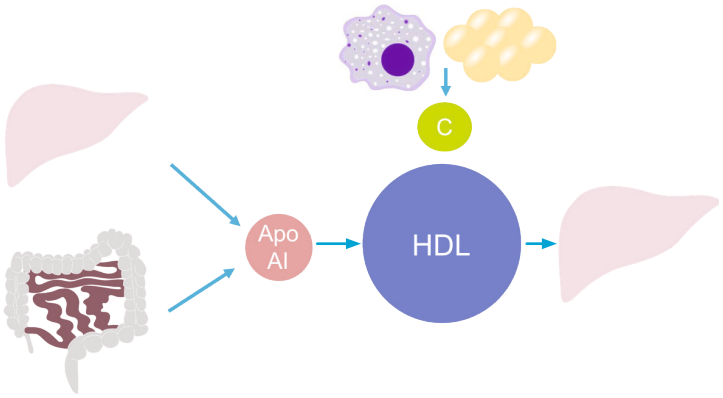
Intestinal pathway



Hepatic pathway

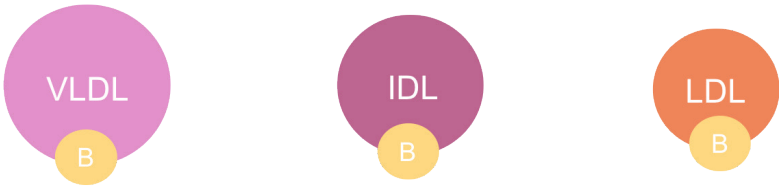


Reverse-cholesterol pathway



Apolipoprotein B-100

VLDL, IDL, and LDL are all carriers of the apolipoprotein B-100. This apolipoprotein is crucial for normal lipid trafficking, as it is recognized by the LDL receptor, which is found on multiple cell types, and is responsible for clearance of these lipoprotein particles from the bloodstream.



SCREENING FOR DYSLIPIDEMIA

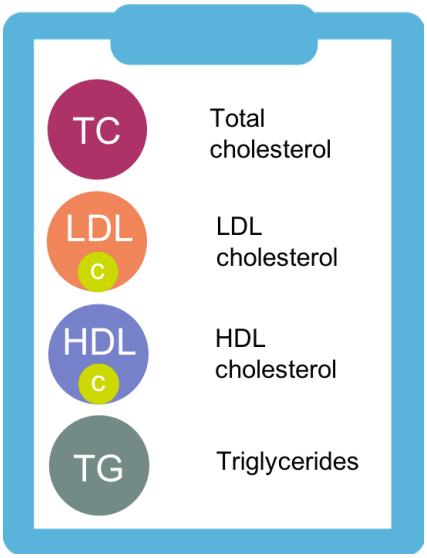
All adults should be screened for dyslipidemia at least once, on their first visit to a primary care facility.

In addition to that first visit, indications for lipid screening include

- Establishing cardiovascular risk in patients with or without known cardiovascular disease
- Monitoring the efficiency of lipid-lowering therapies
- Identifiying familial dyslipidemia
- Determining a potential cause for other clinical problems, like pancreatitis

Basic lipid panel

The basic lipid panel or profile measures four lipids



While TC, HDL-C, and TG are directly measured, in most cases, LDL-C is calculated using the Friedewald equation. Different regions and countries routinely use different units of measurement. Thus, this equation can be used to calculate LDL concentration in either mg / dL or mmol / L.

LDL C = total cholesterol – HDL-C – (triglycerides / 5)

In mg / dL

LDL C = total cholesterol – HDL-C – (triglycerides / 2.2)

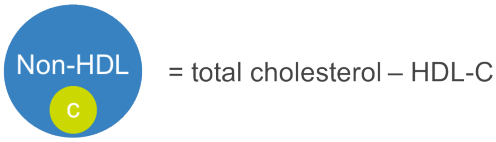
In mmol / L

The Friedewald formula is only applicable if blood was drawn after a fasting period and if triglycerides are below 400 mg / dL or 4.5 mmol / L. If these two conditions are not fulfilled, LDL cholesterol must be measured directly.

There are two additional cardiovascular risk markers that can be calculated

- Non-HDL cholesterol (non-HDL-C)
- Remnant cholesterol

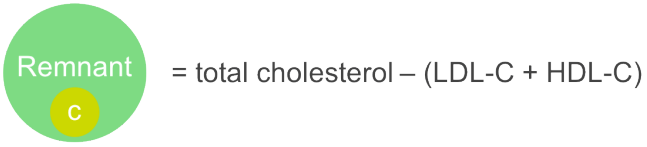
Non-HDL cholesterol



Since you need neither triglycerides nor LDL cholesterol for this formula, it is a useful marker for patients in whom fasting is a problem or in whom triglycerides are too high to use the Friedewald formula to calculate LDL cholesterol.

Non-HDL cholesterol was shown to be as potent as a risk marker as LDL cholesterol in cardiovascular risk assessment.

Remnant cholesterol

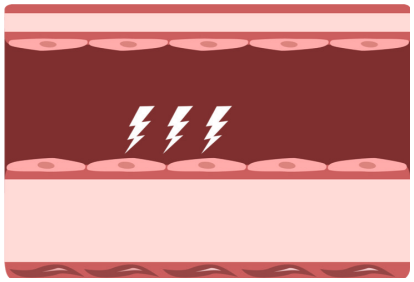


Although remnant cholesterol is causally associated with atherosclerosis, its usefulness for risk assessment or therapy targeting still needs to be evaluated in more detail; therefore, it is not currently included as part of the routine lab set.

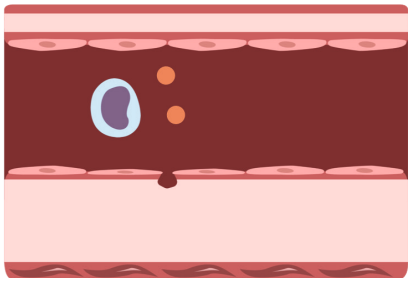
GRASPING THE ROLE OF LIPIDS IN ATHEROSCLEROSIS

The development of atherosclerosis

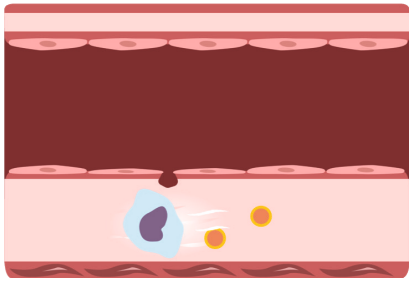
Atherosclerosis is the underlying pathology of cardiovascular disease. The following steps outline the development of atherosclerosis.



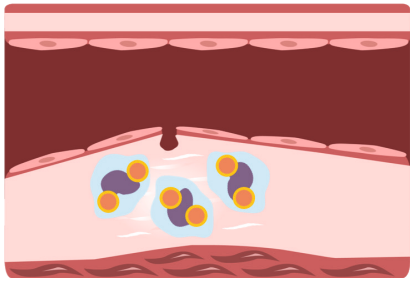
1. Stress exposure



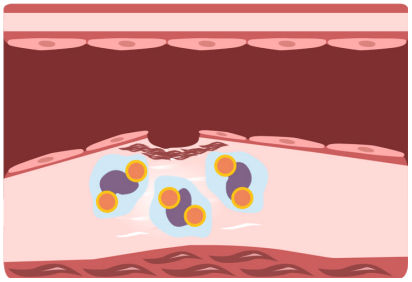
2. Increased permeability



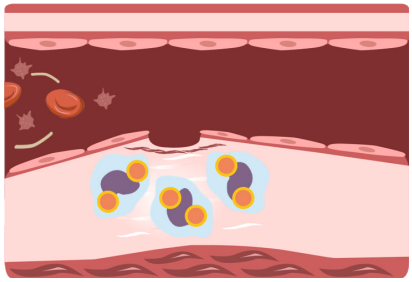
3. Foam cells form



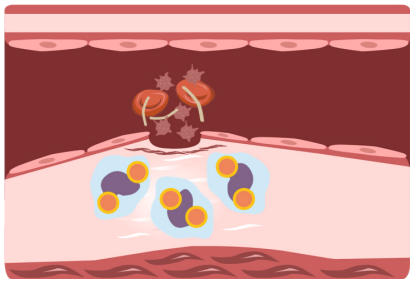
4. Vessel narrows



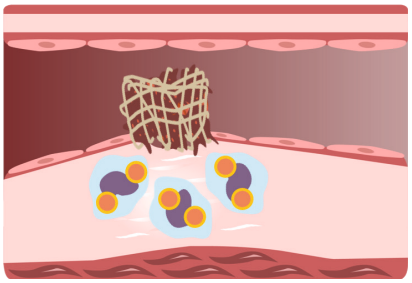
5. Fibrous cap forms



6. Fibrous cap thins



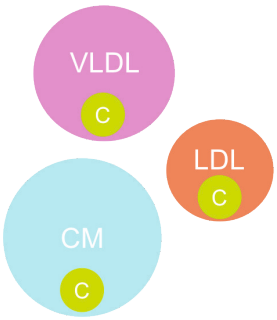
7. Thrombus forms

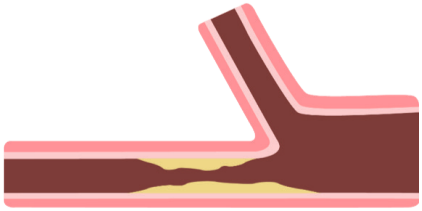


8. Vessel occluded, eliciting acute coronary syndrome

Lipoproteins and atherosclerosis

In addition to LDL, chylomicrons and remnants of VLDL also participate in the development of atherosclerosis. However, we routinely measure only total cholesterol and LDL cholesterol to assess lipid burden and cardiovascular risk.

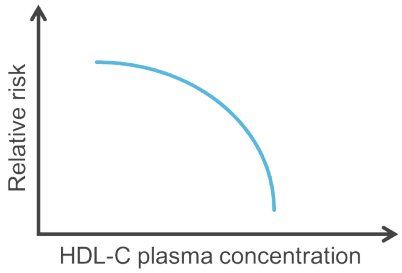




HDL is also thought to be crucial in cardiovascular disease, but unlike other lipoproteins, it is anti-atherogenic. HDL induces macrophage cholesterol efflux, allowing it to clear excess cholesterol from vessel walls. Furthermore, HDL was shown to have anti-inflammatory, antioxidant, anti-apoptotic, and even anti-thrombotic activity, which may also contribute to its anti-atherogenic activity.

In the lab, we measure the cholesterol content of HDL particles, not the number of lipoprotein particles themselves.

Many studies have shown a clear and undisputable role for HDL cholesterol as an independent risk factor for cardiovascular diseases. The lower the HDL cholesterol level, the higher the risk for myocardial infarction, ischemic stroke, and other cardiovascular diseases.

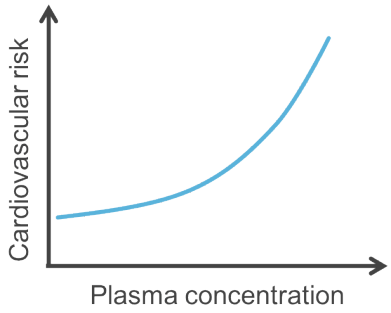


However, increasing HDL cholesterol levels does not reduce the risk of cardiovascular disease and adverse events. This may be because HDL particles do not appear to work properly in an inflammatory environment, like the atherosclerotic vessel wall. Features such as reverse cholesterol transport and the anti-inflammatory actions of HDL are impaired in atherosclerosis.

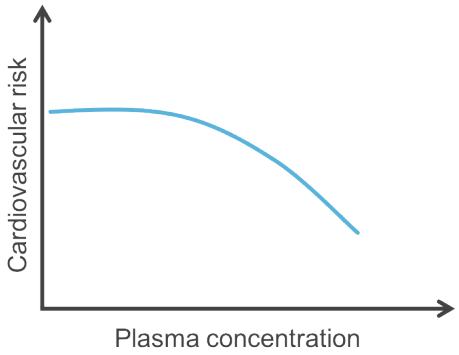
It seems that quality is more important than quantity when it comes to HDL in cardiovascular disease. Therefore, assessing HDL function might be more important than determining HDL cholesterol levels. However, tests that measure HDL function are not widely available. Once we are able to more consistently evaluate HDL function, this marker may become a better target for mitigating cardiovascular disease risk.

ASSESSING LIPIDS IN CARDIOVASCULAR PATIENTS

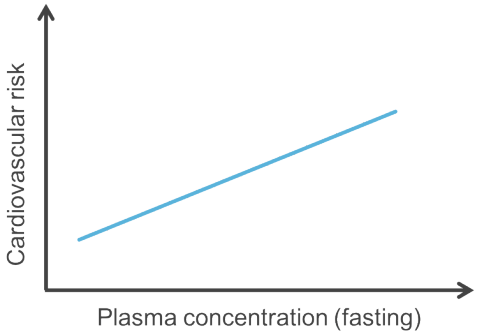
Lipoproteins and cardiovascular risk



There is a significant graded correlation between cardiovascular risk and increasing plasma concentrations of both total cholesterol and LDL cholesterol.



HDL cholesterol has been shown to be anti-atherogenic and is negatively correlated with cardiovascular risk.



Increased levels of fasting triglycerides are associated with increased cardiovascular risk.

Lipoproteins and patient care

Lipoproteins play a crucial role in the assessment of cardiovascular risk as well as in patient treatment.

Risk assessment

There are many different approaches to risk assessment, worldwide. These risk assessment tools calculate the patient's ten-year risk of cardiovascular mortality or non-fatal events.

In Europe, the SCORE risk assessment tool is currently used to assess cardiovascular risk.
The SCORE takes into account the following parameters

- Age
- Gender
- Smoking status
- Blood pressure values
- Your patient's total cholesterol plasma concentration

(**Reference: *Piepoli et al., 2016***)

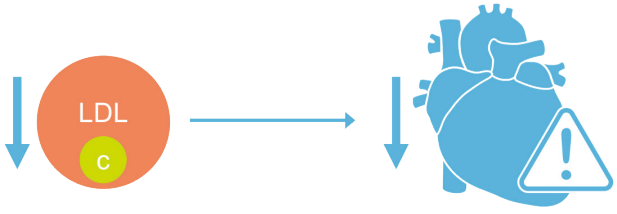
In the United States, the American Heart Association and the American College of Cardiology recommend their own atherosclerotic cardiovascular disease risk assessment tool.
Their risk assessment tool requires the following parameters

- Age
- Gender
- Race
- Smoking status
- Blood pressure values
- Blood pressure treatment
- Whether the patient is diabetic or not
- Total cholesterol levels
- HDL cholesterol plasma concentrations

(**Reference: *Goff et al., 2013***)

Individualized treatment

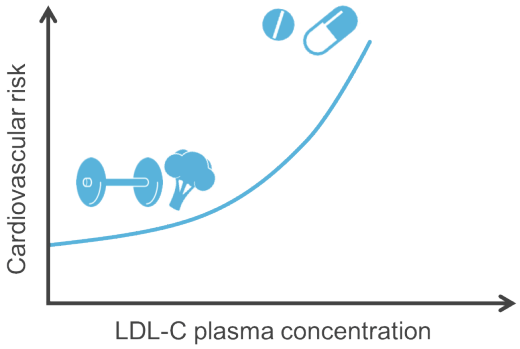
One important therapy goal in cardiovascular risk prevention is to reduce LDL cholesterol levels. Every 1.0 mmol / L (~40 mg / dL) reduction in LDL cholesterol reduces the risk of cardiovascular disease mortality and non-fatal myocardial infarction by 20–25%.



1 mmol / L
(~40 mg / dL)

20–25%

The magnitude of LDL reduction that should be targeted depends on the patient's baseline risk. If their cardiovascular risk and LDL levels are moderate, lifestyle changes might be sufficient. If their risk and LDL levels are high, a more intensive approach involving drug therapy might be more effective.



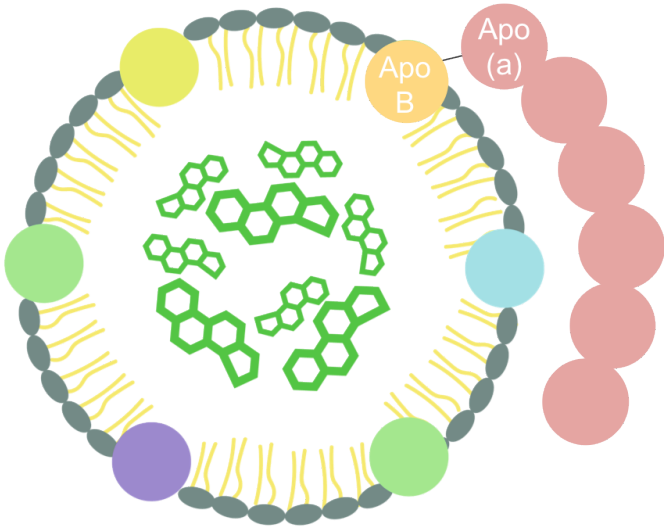
Treatment strategies and lipid target values

Guidelines outlining specific treatment strategies and lipid target values have been published by several different organizations. For more details on these recommendations, please see the guidelines set out by The American College of Cardiology / American Heart Association (**Reference: *Stone et al., 2014***), The European Society of Cardiology (**Reference: *Piopoli et al., 2016***) and the National Lipid Association (**Reference: *Jacobson et al., 2015***).

DISCOVERING ADDITIONAL LIPID MARKERS

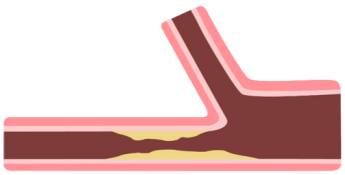
Lipoprotein(a)

Lipoprotein(a) (Lp(a)) is structurally related to LDL with one apolipoprotein B and a similar lipid composition. However, it contains an additional apolipoprotein called apolipoprotein(a).



Lp(a) is thought to be involved in foam cell formation, thus promoting atherosclerosis. Furthermore, apolipoprotein(a) has significant homology with plasminogen and is involved in coagulation: it competes with plasminogen in binding to cells, which leads to decreased plasminogen activation and consequently impaired fibrinolysis.

Features of Lp(a)



Pro-atherogenic

Pro-thrombotic

Clinically, Lp(a) excess is a modest, but independent risk factor for cardiovascular disease, especially premature coronary heart disease, and is associated with the presence of complex lesions.

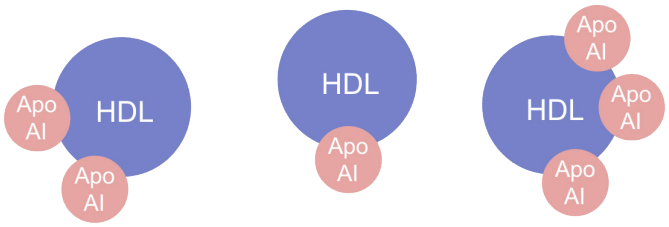
It is not necessary to screen the general population for Lp(a). Screening can be useful in intermediate to high-risk cardiovascular patients without any other dyslipidemia, in patients with premature cardiovascular disease or a strong familial history of coronary artery disease, or in patients who do not respond to therapy for lowering LDL cholesterol.

Since Lp(a) concentrations are genetically determined and not dependent on lifestyle, it is sufficient to measure Lp(a) once in a patient's lifetime.

Apolipoproteins A1 and B-100

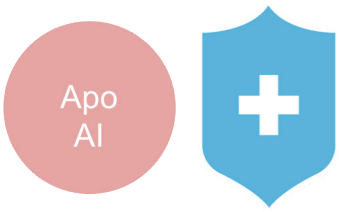
Apolipoprotein A1

Apolipoprotein A1 is the major apolipoprotein in HDL particles. It is involved in cholesterol efflux from cells and esterification of cholesterol. Since the number of ApoA1 proteins varies per HDL particle, ApoA1 does not reflect HDL particle numbers 1:1.



ApoAI ≠ HDL particles

High ApoA1 levels are protective against cardiovascular disease.



Apolipoprotein B-100

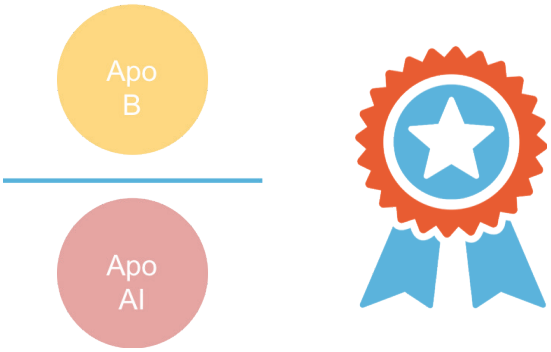
Apolipoprotein B-100, often abbreviated in lab tests as ApoB, is the main apolipoprotein of pro-atherogenic lipoproteins like LDL, IDL, VLDL, and Lp(a). Since each LDL particle only carries one ApoB protein, ApoB levels can be used as a surrogate for circulating LDL particles.

ApoB ≈ LDL particles

High ApoB levels are associated with increased risk of cardiovascular disease.

ApoB : ApoA1 ratio

The ratio of ApoB : ApoA1 is the most powerful diagnostic tool regarding these two apolipoproteins. This ratio was shown to be superior for risk prediction when compared to ApoA1 or ApoB alone. Interestingly, the ratio is also a better predictor of cardiovascular risk than either LDL cholesterol or HDL cholesterol.



In addition to being a powerful risk marker, apolipoprotein testing has the advantage of not requiring fasting.

One situation where apolipoprotein testing is clearly recommended is when the patient's lipid panel results are strikingly unremarkable for the given cardiovascular risk or positive medical history.
Sometimes apolipoproteins uncover the underlying lipid disorder when the basic panel cannot.

THINKING ABOUT DIFFERENTIALS

Dyslipidemia can result from primary or secondary causes.

Primary causes

Monogenic lipid disorders

Familial hypercholesterolemia

The most prevalent monogenic lipid disorder is familial hypercholesterolemia, which affects about 1 in 200–300 individuals in Europe and the United States, in its heterozygous form. The functional mutation lies within one of several genes involved in LDL metabolism, and affects the removal of LDL from the blood.

This disorder is characterized by a higher risk for cardiovascular events than in the general population, especially before the age of 40.

In the lab report, extremely elevated LDL cholesterol levels (above 190 mg / dL or 4.9 mmol / L) along with normal HDL cholesterol and triglyceride levels are characteristic of this disorder.

However, if the patient has other risk factors, such as obesity or diabetes, elevations in triglycerides may be present and do not rule out familial hypercholesterolemia.

Clinically, cholesterol depositions in the skin, tendons, and arteries are often seen. The depositions in skin and tendons are called xanthomas.

When clinical findings and lab results suggest familial hypercholesterolemia, genetic testing may not contribute substantially to the diagnosis. Genetic testing is more important in asymptomatic patients with a positive family history. However, the need for genetic testing should be discussed with a lipid specialist.

Polygenic lipid disorders

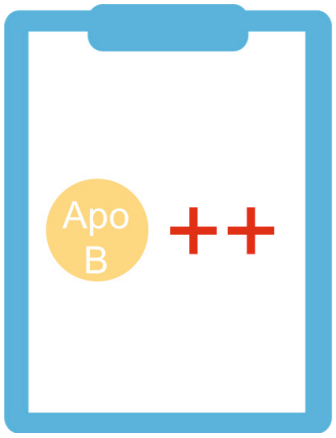
There are a variety of polygenic lipid disorders.

Polygenic hypercholesterolemia

Polygenic hypercholesterolemia is very common. It can be hard to distinguish from monogenic familial hypercholesterolemia, but characteristic xanthomas are usually missing. The disorder is diagnosed based on clinical presentation and family history.

Familial combined hyperlipidemia

In familial combined hyperlipidemia, lipid abnormalities can vary with patients showing elevated total and LDL cholesterol, elevated triglycerides or both. Apolipoprotein B levels are often increased.



Clinical signs like xanthoma are usually missing in this disorder, but the incidence of cardiovascular disease is high. Patients are diagnosed based on clinical presentation and family history.

Secondary causes

In contrast to primary dyslipidemia, which is inherited and genetic, secondary dyslipidemia develops as the result of the presence of another pathology. About one quarter of patients referred to a lipid clinic will have one or more secondary causes to be dealt with.

Common causes of secondary dyslipidemia

- Hypothyroidism
- Diabetes mellitus
- Obesity
- Excessive alcohol consumption
- Renal disorders like nephrotic syndrome or chronic renal failure
- Cholestatic liver disorders like primary biliary cholangitis
- Chronic use of drugs like steroids, beta-blockers, thiazide diuretics or anticonvulsants
- Use of oral estrogens
- Polycystic ovary syndrome

Acute and transient secondary causes of dyslipidemia

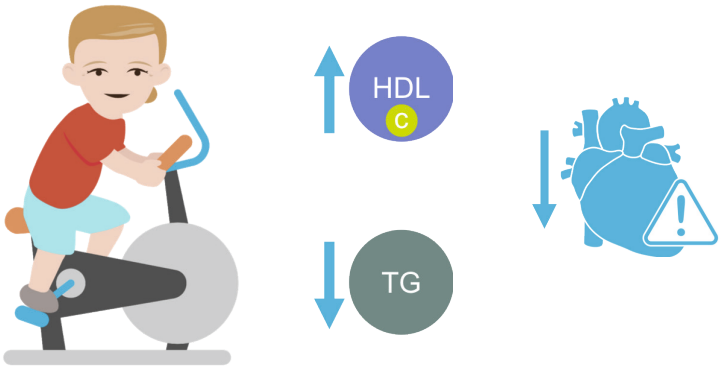
- Pregnancy
- Trauma
- Surgery
- Burns
- Severe bacterial and viral infections

In acute and transient situations, lipid screening might be postponed if clinically feasible.

CHANGING DIET AND LIFESTYLE

Unhealthy diet and lifestyle habits contribute to dyslipidemia. Consequently, diet and lifestyle changes should be advised to every individual with lipid abnormalities.

Although there are currently no target levels available for triglyceride and HDL cholesterol levels, lifestyle changes will improve HDL cholesterol and triglyceride profiles and will decrease cardiovascular risk.



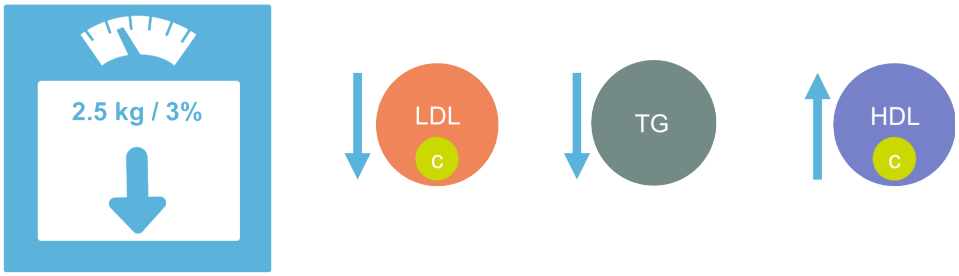
Healthy diet

Consuming vegetables, fruits, whole grains like rye / oats / barley, low-fat dairy products, poultry, fish, and legumes should be a priority. Patients should also be encouraged to favor unsaturated fatty acids, especially polyunsaturated fats, such as those that can be found in vegetable oils and nuts.

Eating saturated and trans fats should be avoided. This includes deep-fried food, frozen dinners, cookies, pastries, crackers, popcorn, etc. Coconut oil should also be avoided, as it has been shown to raise LDL cholesterol. (**Reference: *Maki et al., 2018***)

Weight loss

A maintained weight loss of at least 2.5 kg or 3% of the body weight was shown to decrease LDL cholesterol as well as triglyceride levels and to increase HDL cholesterol levels.



A high level of physical activity, eating breakfast regularly, self-monitoring of weight, and consistent calorie-controlled eating patterns support maintaining the weight loss.

Physical activity

In order to have a significant favorable effect on lipid profiles as well as on body weight, individuals should undertake 30–60 minutes of moderate to intensive aerobic exercise daily.

Resistance exercise to maintain strength, balance, and bone density is equally important.

Lipid-lowering supplements

Plant sterols

A number of plant sterol supplements are commercially available in margarines, juices or powders. Studies have shown a LDL-lowering effect of these supplements. While these results seem promising, more evaluation and clinical endpoint studies are needed before these products can be more widely recommended for use as lipid-lowering therapy.

Red yeast rice

Red yeast rice is a fermented rice product that is used in Chinese medicine. It contains monacolins that decrease LDL levels through the same mechanism as statins. However, the currently available products generally lack standardization in monacolin concentrations. For this reason, they are currently not recommended for use in treating dyslipidemia.

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