Lesson 3: Dyslipidemia

- **Hypercholesterolemia** refers to an increase in total plasma concentration of cholesterol. This total cholesterol is combined LDL, HDL, and VLDL. CM or IDL have short half-lives, so when we measure cholesterol levels in fasting patients, the amount present is insignificant. According to the guidelines by the **National Cholesterol Education Program or NCEP**, total cholesterol below 200 mg/dL is considered desirable. Levels between 200 and 239 are considered borderline high, and anything above 240 is abnormally high. These numbers are usually just a starting point, when it comes to evaluating a patient, and it is normally necessary to look at the individual cholesterol components—i.e. LDL, HDL, and VLDL.

- LDL is the major source of cholesterol. In fact, anywhere between two thirds and three quarters of the cholesterol is present within LDL. VLDL makes up a small amount of plasma cholesterol, which is around 10 to 15 percent. HDL carries 20 to 30 of the total plasma cholesterol, but since HDL cholesterol is actually removed from tissues, this is a good number.

- Total cholesterol is the sum of LDL, HDL, and VLDL cholesterol, so we can rearrange the equation to say that **LDL is total cholesterol minus HDL minus VLDL**. Total cholesterol and HDL cholesterol are easily measured. VLDL cholesterol on the other hand is approximated from total triglycerides. Since VLDL is mostly triglycerides, then VLDL cholesterol considered to be roughly a fifth or 20% of the total triglycerides. Thus, we can plug this value in and derive a new equation where LDL equals total cholesterol minus HDL cholesterol minus 0.2 times or 20% of the total triglycerides. One caution to consider is if TG is >250 mg/dL, LDL is underestimated.
here is that the VLDL cholesterol is estimated from total plasma triglyceride level, and this works fine for most people, but if you have an individual with hypertriglyceridemia or if the TG levels are greater than 250, then the VLDL cholesterol would overestimated and LDL would be underestimated. In that case, we need to modify the formula slightly so that VLDL cholesterol represents say 15% of the total triglycerides instead of 20%. In any case, there are new techniques that yield more accurate numbers, but this methodology is still widely accepted.

- Since LDL cholesterol is the major problem, let's take a look at the numbers. For most individuals, **LDL levels below 130** are considered normal. However, for people who are at risk of cardiovascular diseases, this is dropped to less than 100. Patients who already have a heart condition or are at **very high risk due to other related conditions** are advised to bring down the level to below 70.

- LDL has a long half-life, so it is directly responsible for the atherosclerotic damage that is central to most cardiovascular diseases.

- The only significant way in which LDL level is kept from getting too high is through uptake by hepatocytes. So think of **the liver as the sink for LDL removal**. Quite obviously then, defects in this uptake or internalization process will translate into high LDL levels in plasma.

- Functional LDL receptor is critical for lowering LDL-C.

- **Primary hypercholesterolemia** can be divided into three major category. There is **familial hypercholesterolemia** which itself can be divided into three sub-categories depending on the specific mutation or defect. There may be mutations within the LDL receptor itself or the

<table>
<thead>
<tr>
<th>LDL-Cholesterol (US)</th>
<th>LDL-Cholesterol (Canada, Europe)</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;70 mg/dL</td>
<td>&lt;1.8 mmol/L</td>
<td>For people at very high risk of heart disease</td>
</tr>
<tr>
<td>&lt;100 mg/dL</td>
<td>&lt;2.6 mmol/L</td>
<td>For people at risk of heart disease</td>
</tr>
<tr>
<td>100-129 mg/dL</td>
<td>2.6-3.3 mmol/L</td>
<td>Within ideal range</td>
</tr>
<tr>
<td>130-159 mg/dL</td>
<td>3.4-4.1 mmol/L</td>
<td>Borderline High</td>
</tr>
<tr>
<td>160-189 mg/dL</td>
<td>4.1-4.9 mmol/L</td>
<td>High</td>
</tr>
<tr>
<td>&gt;190 mg/dL</td>
<td>&gt;4.9 mmol/L</td>
<td>Very High</td>
</tr>
</tbody>
</table>

* LDL-C levels related to atherosclerotic progression

---

**Primary Hypercholesterolemia: Causes**

1. Familial hypercholesterolemia (FH)
   a) defective LDL-R
   b) defective apoB100
   c) pcsk9 gain of function mutations

2. Autosomal recessive hypercholesterolemia (ARH)
   - defective ARH adapter protein

3. Polygenic hypercholesterolemia
   a) majority of cases
   b) undefined (or many) underlying defects
apoB100 apoprotein, or a protein called pcsk9.

- A related form of hypercholesterolemia is known as **autosomal recessive hypercholesterolemia or ARH**, and in fact the protein that is defective here was named after this condition. Finally, there is a third type of hypercholesterolemia that is actually the most common type. Here the actual defect may be present within several genes and we don't know the identity of the genes or the underlying mechanisms. So this is known as **Polygenic Hypercholesterolemia**.

- The most common sub-category within this group is caused by **defects within the LDL receptor itself**. Recall that it is the LDL receptor that first serves as the docking site for the LDL particle and is involved in the uptake process. The LDL particle binds to the LDL receptor via apoB100 apoprotein and then it is internalized. So when it comes to LDL receptor, mutations can have an impact on many points. For example, there may be a **defect in LDLR synthesis**, so that LDLR expression at the cell surface is simply not enough, even though the actual uptake process is fine. Another possibility is that **LDLR is synthesized but there is a defect in the process that sends the receptor to the plasma membrane**. There may be **mutations within the receptor that reduce its affinity for apoB100**, so we get decreased interaction between the receptor and LDL. Finally, there may be other mutations that don't interfere with the binding between the two but the internalization process is compromised, so we don't get enough LDL uptake. In summary, any genetic defect that affects synthesis, localization, binding affinity, and internalization of the LDLR will result in high plasma levels of LDL.

- Genetic defects within the gene encoding the LDL receptor can be of two types. Patients who carry one defective copy but have one normal copy of the gene are **heterozygous**. This is relatively **common and one in 500 individuals in the...**
**United States** fall into this category. Because they have only one functional copy of the gene, they would have fewer LDL receptors at the cell surface resulting in higher plasma LDL cholesterol. The LDL cholesterol levels tend to be in the range of 275 to 500, resulting in increased cholesterol deposits within tissues, particularly in tendons in form of xanthomas. These patients also have an increased risk of coronary heart disease as a result of the high LDL levels. However, they do respond to drugs, including statins, if they are identified early enough, so they are often referred to as “responders”.

- Individuals who are homozygous for this defect have both copies of the LDLR gene defective, so they have complete absence of functional LDLR. Obviously, this is a more serious form than the heterozygous, but Fortunately it is found in only one in a million people. These patients tend to have extremely high LDL levels, which typically range between 700 and 1200. Unfortunately, they don’t respond to statins, so they are referred to as “non-responders” which distinguishes them from the above group. Patients are found to have evidence of coronary heart disease before they reach their 20’s.

- When it comes to Familial Hypercholesterolemia, it is possible that the LDL receptor is functional but LDL particles fail to bind to the receptor because of defects in apoB100 apoprotein. LDL doesn’t have apoE so it is completely dependent on apoB100 for docking with LDL receptor. Compared to defects in LDL receptor, apoB100 mutations are relatively less common, occurring on average at 1 in 1000 people. These autosomal dominant defects result in decreased affinity for the LDL receptor and reduced rate of LDL
internalization. Of course, this causes an increase in LDL levels and predisposes one to increased risk of coronary heart disease.

- Finally, the third type of defect that is seen in Familial Hypercholesterolemia is in the gene encoding **PCSK9**. PCSK9 is a serine protease that hydrolyzes the LDL receptor and reduces the number of receptors on the cell surface. Gain of function mutations that increase PCSK9 activity will reduce the number of LDL receptors expressed at the surface of the cells. This will increase LDL-C levels.

- **Autosomal Recessive Hypercholesterolemia** or ARH has been known for a long time and sometimes it is even grouped together with Familial Hypercholesterolemia. Here the defect occurs within the gene encoding an adapter protein known as ARH. In fact, they named the protein after the condition itself. This protein is critical for the LDL receptor internalization machinery, so if it is defective then the process of endocytosis will not occur and LDL will not be removed from plasma. But the LDL particles can still bind to the receptor, so it does remove some LDL from the plasma and it is not as severe as the homozygous form of familial hypercholesterolemia, particularly since statins do have some beneficial effects here.

- The most common cause of hypercholesterolemia polygenic, meaning that there is no single recognizable or defined defect. Rather, hypercholesterolemia typically arises as a result of **multiple genes**. These genes are usually undefined but likely play a role in lipid metabolism. Also, the genes that are responsible for this type of hypercholesterolemia do not necessarily harbor any specific mutations. Rather, it is the **expression of these genes that changes**. The **change in expression disrupts**
the lipid homeostasis, which ultimately results in high LDL cholesterol levels. Most often, these changes occur with aging as well as with changes in diet and lifestyle. Since there is no specific mutation involved, the actual machinery involved in LDL endocytosis remains functional, so this type of hypercholesterolemia is fairly treatable, particularly with statins.

- In contrast to primary hypercholesterolemia, secondary hypercholesterolemia arises as a consequence to a disease or drug treatment. Some of the most common causes of secondary hypercholesterolemia include hypothyroidism, obstructive liver disease or kidney diseases. Corticosteroid therapy and HIV protease inhibitors are some of the most common drugs that can cause secondary hypercholesterolemia.

HYPERTRIGLYCERIDEMIA (HTG)

- Hypertriglyceridemia is another common form of dyslipidemia. In this case, there is an increase in plasma triglyceride levels instead of cholesterol. When it comes to TG levels, anything below 150 is considered desirable. Between 150 and 200 is considered borderline high, between 200 and 500 is considered high, and anything over 500 is very high. A word of caution here though that unlike cholesterol levels, TG levels tend to fluctuate substantially in some people depending on diet or medications they may be taking. For example, in some people a single drink of alcohol can send the TG levels close to 500. So the diagnosis of hypertriglyceridemia should be made only after underlying causes have been first addressed.

- There has been some debate about the exact role of TG levels in coronary heart disease because unlike cholesterol where we know the molecular pathology, the mechanistic basis for how TG could contribute to atherosclerosis is not entirely clear. In any case, now it is understood that hypertriglyceridemia represents an independent risk factor for heart disease and must be addressed.
Hypertriglyceridemia can be classified into **four major categories**. There are **two types of familial HTG**.

1. The first type of **familial HTG** is an autosomal dominant form that is relatively common. It is a form of HTG where there is a **mild to moderate increase in TG levels** but the LDL-C levels are usually within the normal range, although HDL cholesterol may be reduced slightly. Even though this is an inherited defect, usually there is no definitive family history of heart disease. Mechanism is not very clear, but it is thought that these individuals harbor a defect in bile metabolism leading to overproduction of bile acids. This triggers the liver to increase the production of VLDL, which of course is the major source of TG. The result is one gets mild to moderate increase in the plasma TG levels which are generally **asymptomatic**.

2. **The second type of familial HTG** is an autosomal recessive form that is caused by a **mutation in the gene encoding Lipoprotein Lipase**. Defective LPL would be unable to remove the TG content from lipoproteins, resulting in profound increase in plasma TG levels. These high TG levels can cause eruptive skin lesions known as **xanthomas** as well as **pancreatitis**.

3. The third type of familial HTG is caused by mutations in the gene encoding **apoprotein apoCII**. LPL is normally inactive and is activated by apoCII when the lipoprotein comes in contact with tissues. In the absence of functional apoCII, **LPL is not activated** and therefore does not remove TG from the lipoproteins. Therefore, mutations in apoCII are **indistinguishable from mutations in LPL** because the effects are the same, but mutations in apoCII are relatively rare.

4. The most common form of hypertriglyceridemia is a multigenic form that develops later in life. It is associated with **weight gain**, particularly around the waste, and diabetes. Typically there may be a **slight increase in LDL cholesterol** and a reduction in HDL cholesterol, so it is a part of what is known as **mixed hyperlipidemia**.
• **Dysbetalipoproteinemia:** This is a form of dyslipidemia where there is an increase in CM & IDL in plasma. Since these two particles are rich in TG, the total plasma TG increases as well. In these patients there is an **underlying defect in the apoE gene.** Since apoE is required for uptake of these particles by the liver, the defect results in an increased half-life of these lipoproteins. Even though the mutation is present at birth, the actual condition does not show up until the patients are in their 50’s. In terms of treatment approaches, diet and exercise in combination with niacin or fibrates is most often the recommended approach.

• **Secondary HTG:** The following table summarizes the most common diseases and drugs that trigger HTG:

<table>
<thead>
<tr>
<th>Disease</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>Alcohol</td>
</tr>
<tr>
<td>Chronic Renal Failure</td>
<td>Corticosteroids</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Estrogen</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>Beta-blockers</td>
</tr>
<tr>
<td>Sepsis</td>
<td>Diuretics</td>
</tr>
<tr>
<td>SLE (lupus)</td>
<td>HIV Protease Inhibitors</td>
</tr>
</tbody>
</table>

**LOW HDL-C LEVELS**

• Low HDL-C levels are known to be an independent risk factor for coronary heart disease regardless of the LDL-C levels. The most common cause of low HDL-C are obesity and early diabetes or insulin resistance that are part of the metabolic syndrome. Rarely, though, low HDL-C are caused by genetic mutations in one of three genes—**apoA1, ABCA1, or LCAT.** Depending on which protein is defective, HDL particles either fail to assemble or mature, or they may not functional optimally because they cannot remove cholesterol from tissues.

• **ApoA1 Defects:** apoA1 is required for the **assembly** of the HDL particles as well as for the **reverse cholesterol transport** or efflux of cholesterol from cells. So if the
defect in apoA1 is severe enough then there will be no HDL formation. More often though, there are mutations that decrease apoA1’s functionality so that it is not very efficient, in which case there is low HDL-C in circulation that is associated with an increase in risk of coronary heart disease. In fact, several studies have shown that there is an inverse relationship between plasma apoA1 levels and coronary heart disease, so higher the apoA1 level better.

**ABCA1 Deficiency**: ABCA1 is required for the assembly of HDL as well as for the efflux of cholesterol from cells. As with apoA1, people with mutations that reduce ABCA1 function tend to have lower HDL cholesterol levels, which increases their risk of coronary heart disease. In more severe cases which are fortunately very rare, ABCA1 is either absent or completely non-functional, resulting in very few HDL particles. Tangier's disease is one such example where there is severe ABCA1 deficiency. In absence of HDL, tissues accumulate cholesterol levels and extremely high cholesterol levels tend to cause cell death in these tissues. Nerve damage results in a form of neuropathy that is usually one of the early signs of the disease. High cholesterol levels also cause coronary heart disease as well as stroke in these patients at a very early age. Fortunately, this is a very rare disease and only about 100 cases have been identified so far.

**LCAT Deficiency**: When HDL particles are first assembled, they are shaped like a disk because they do not have CE or TG at the core and contain only phospholipids and free cholesterol at the surface. These particles are not very effective at removing cholesterol until they mature and develop the core. This maturation process depends on the enzyme LCAT. LCAT esterifies the cholesterol at the surface so that the ester form moves to the core. Defects in LCAT result in a condition where HDL particles in the blood are premature and disk shaped. Since they are not as effective as the fully formed HDL particles in removing cholesterol from cells, there is an increased risk of atherosclerosis in patients with this defect. Patients with this defect are often said to have the “fish eye disease” because there is cholesterol deposits within the cornea that gives it an opaque appearance that resembles a fish’s eye.

**Correction of low HDL-C levels**: Unlike with LDL cholesterol and triglycerides, pharmacological approaches to correcting HDL-C levels are not always effective. Of course, correcting the underlying medical issues such as hypertension and diabetes would be the first critical step in patients with these conditions. Also, low HDL-C
levels are usually a part of the **mixed hyperlipidemia** that is seen in **metabolic syndrome**, **proper diet** and **exercise** are also helpful. Some studies have shown that one to two alcohol drinks a day increases HDL cholesterol, but this has to be balanced with complications related to TG levels. Also, patients who are **smokers** **invariably see their HDL-C levels rise when quit smoking**, so all these factors are useful in correcting this problem. HDL-C should not be looked at in isolation. In fact, it is the **total cholesterol to HDL cholesterol ratio** that is also important. This ratio is considered favorable when it is kept **below 3.5**, but as it rises **above 4.5 the risk of coronary heart disease increases significantly**. Drug treatment to lower LDL-C is usually successful in correcting this ratio.