Cholesterol

A Re-introduction To Cholesterol & Heart Disease For All Ages

- TheFatNurse
Before reading, please understand I am not an expert in this field. The subject matter of cholesterol and heart disease came from personal interest in discovering mixed messages between the research and clinical advice.

I have to heavily thank the terrific work of people such as Thomas Dayspring M.D., Tara Dall M.D., William Cromwell M.D., Brian Edwards M.D., and Peter Attia M.D. for introducing me to such a complex, fascinating, and important area of study. This comic is designed solely to pique your interest and by no means covers even a fraction of what these individuals have to offer.

Additionally, it is important to acknowledge the many pioneers in the field such as John Gofman M.D., Pete Ahrens M.D. and Ronald Krauss M.D. Their contributions are slowly becoming more well known and a new golden age in the study of heart disease and lipids is coming.

If anything in this comic is of interest please look up the individuals mentioned above.

- TheFatNurse R.N.
6/6/2012

***This comic is meant for educational purposes only and not clinical advice. Consult with your primary care provider if you have any medical questions or plan on making any changes to your diet***
Meet Cholesterol. Cholesterol is a very sad organic molecule because everyone hates him.

Of course we hate him! He does nothing but clog our arteries and try to kill us!

TFN: Can you please let me finish the story...

We already know this story. Eat less fat. HDL is good. LDL is bad!

TFN: Its not quite that simple...I mean do you even know what cholesterol does?

0...uhh...

TFN: Alright, lets start this story from the very beginning...

This is what cholesterol is. Don't worry about the chemistry stuff for now.

Every cell in our body needs it in the membrane to exist

We DIE WITHOUT IT

It also plays a role in helping make vitamins, hormones and bile

Well yea of course! But if we eat too much of it then we get clogged!

TFN: Again not that simple...back to the story

It keeps our bodies running

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Cholesterol can be unesterified (UC) or esterified (CE).

In other words, the body wants cholesterol in a certain range. If you eat less cholesterol your body will make more or reabsorb more!

This is important because the body regulates cellular cholesterol through cholesterol homeostasis.

Too much cellular cholesterol leads to crystalization and apoptosis (cell death).

This cellular cholesterol is not the same as plasma cholesterol which is what your doctor may collect.

Here's an example of this balance with absorption of cholesterol in our gut:

Getting to the Gut has been my dream foevva!

Try to think of this as a University. See those UC cholesteroles above? Think of them as students.

The cells in the gut have a special protein called NPC1L that will let UC students inside.

However another protein administrator called ABCG5/ABCG8 will kick them out if they are bad students or if they already accepted enough students for the new semester.
-Wait what about that other kind of cholesterol? CE?

TFN: Well here's the thing. The body can only absorb UC in the gut!

CE: No one wants to play with me...

This is important because most of the cholesterol we consume is CE! This means most of the cholesterol we consume isn't absorbed!

Most?

TFN: there are lipases that could change CE into UC for absorption, but this still amounts to a minority

Lipase: Hey CE wanna become a UC?

CE: OMG! Get away!

Wait...if the amount of cholesterol we eat doesn't matter...why do they say not to eat more than 300mg?

TFN: Well some countries like Canada have gotten rid of their national recommended cholesterol intake!

Most of the cholesterol in our body is endogenous - we make it ourselves!

Liver: Gonna make some cholesterol today cause we need it!

***cells outside the liver (extrahepatic) actually make most of the cholesterol

Therefore, dietary cholesterol's impact on the cholesterol in your body is not that significant

Things will get a litte more complicated next with HDLs, LDLs. However some kittens will help clarify things.
Hello! I am the Kittehz. I'm only here cause TFN promised a kittehz. Today's comic can be a little dense but-

TFN: Okay that's enough of you! <kick>

I hate you TFN!

Cholesterol is like this more relevant kittehz. It has hydrophobic properties that make it afraid of water like the plasma in our blood.

Just like Captain Kittehz, it needs a ship to sail around the plasma. This ship is a protein and when traveling with cholesterol it is known as a lipoprotein. Sound familiar right? Lipoprotein is the the last "L" in HDL and LDL.

We need just a little bit more detail tho. To the left is a lipoprotein. The proteins that collect the fatty lipids are called apoproteins. Once these apoproteins are bound to lipids they are called apolipoproteins.

The Lipoprotein is the protein that transports this entire thing.

Apolipoproteins help the lipoprotein with structural integrity and solubility. Additionally they also serve as co-factors in enzyme reactions and help the lipoprotein interact with receptors on other cells.

There is even more significance to the apolipoproteins: Identification. Most Apolipoprotein B (ApoB) is found in LDL and most Apolipoprotein A1 (ApoA1) is found in HDL.
Okay TFN, you explained to me what the "L" in HDL and LDL is, but what about the "D"?

TFN: My dear sir, your inquiry shows you are not that "dense." Ah ha-ha I made a pun. <sips tea like a sir>

In case you didn't pick that up, the D in HDL/LDL stands for density and represents the ratio between lipid and protein defined as mass per volume.

Remember the Lipoprotein is composed of proteins and lipids on the outside membrane and inner core. See picture on previous page! Proteins are usually denser than fats.

The H and L in HDL/LDL therefore stand for High or Low Density!

Below is a graph borrowed from Peter Attia MD that breaks all of this down:

<table>
<thead>
<tr>
<th>Density (g/mL)</th>
<th>Class</th>
<th>Diameter (nm)</th>
<th>% protein</th>
<th>% cholesterol</th>
<th>% phospholipid</th>
<th>% triacylglycerol&amp;cholesterol ester</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;1.063</td>
<td>HDL</td>
<td>5-15</td>
<td>33</td>
<td>30</td>
<td>29</td>
<td>4</td>
</tr>
<tr>
<td>1.019-1.063</td>
<td>LDL</td>
<td>18-28</td>
<td>25</td>
<td>50</td>
<td>21</td>
<td>8</td>
</tr>
<tr>
<td>1.006-1.019</td>
<td>IDL</td>
<td>25-50</td>
<td>18</td>
<td>29</td>
<td>22</td>
<td>31</td>
</tr>
<tr>
<td>0.95-1.006</td>
<td>VLDL</td>
<td>30-80</td>
<td>10</td>
<td>22</td>
<td>18</td>
<td>50</td>
</tr>
<tr>
<td>&lt;0.95</td>
<td>Chylomicrons</td>
<td>100-1000</td>
<td>&lt;2</td>
<td>8</td>
<td>7</td>
<td>84</td>
</tr>
</tbody>
</table>

Here are some representations of these classes:

**HDL: Mighty Mouse**

HDL is the smallest of the classes but also packs the most percent of protein with the least triglyceride.

This representation does not imply HDL is "healthy".

**LDL: EggMan**

LDL has the most percent of cholesterol compared to the other classes.

**IDL: Change Sign**

IDL is moving towards change. It will eventually become either an LDL or get cleared out by the liver.

**VLDL: Liver man**

Traffics triglycerides from the liver.

**Chylomicron: Skunk**

Traffics triglycerides from the intestine.
Umm...that's great but how does it all work?

Well let's start with the biggest one: Chylomicrons

Chylomicrons transport lipids from the gut to adipose, cardiac, muscle and the liver.

In the liver we will now move to VLDLs which are exported here to traffic triglycerides.

Now usually the only lipoproteins that are talked about are the LDLs and HDLs. But did you know that the VLDLs are actually the precursor to LDLs? It works like a set of Russian dolls:

As the bigger VLDL 6 is traveling around the body, it gives up a bit of its triglycerides (TGs) in the form of fatty acids for use in the body with surface phospholipids similar to a set of Russian dolls being removed. Like the dolls, it eventually gets smaller and smaller through this process until it becomes IDL and then potentially LDL.

Most IDLs then get cleared by the liver but some continue to shrink and become LDLs!
As LDLs are getting smaller by giving off their TGs and cholesterol, it's traditionally thought that HDLs come by and return these things back to the liver - termed reverse cholesterol transport. This is why HDL is often thought of as a "good guy." However, this is outdated and it now appears that LDL does this with HDL as a helper along this metabolic pathway!

"Wait so LDLs is a good guy now?"

TFN: No it's both! The good guy bad guy classification was wrong to begin with!

The trouble occurs when these LDLs, classified as LDL particles (LDL-P) crash through an artery wall and deposit their cholesterol into the artery (LDL-P are the cars and cholesterol are the passengers!)

There is a lot more to this story than just crashing and causing plaque, but for simplicity we'll skip things like foam cells and just say too many crashes will lead to atherosclerosis.

Well no worries about plaque anyway, my cholesterol is A-OK last time I checked

TFN: No Listen! That's what I'm trying to tell you! Your regular lipid profile only tells you the amount of passengers (cholesterol) and not the cars! (particles). It's not as accurate as we think!

W...w... WHAT!?
TFN: The labs we draw today, are collecting the cholesterol content (HDL-C/LDL-C) not the particles! Remember, we want to know how many cars, not how many passengers!

How on earth did we come to rely on these measurements then!?

TFN: Yeah by going online!

Gawd I hate you

TFN: That's an interesting question and one we need to travel back in time to answer

You're telling me time travel is possible as well too!?

In the 1950s John Gofman used an ultracentrifuge to discover the lipoprotein classes as we know them today.

While this was important, there was no way anyone in the country could access an ultracentrifuge at the time. Testing had to rely on traditional testing which was LDL-C, HDL-C and triglycerides

What!? Then what is all that talk of saturated fat, LDL and heart disease I was told!? Doesn't that matter? Where is the particle theory in that!?

Remember, we want to know the cars (lipoprotein particles) and not the passengers (cholesterol)

When getting our cholesterol readings, we would have to break open the cars to get to the people. This violent force left us with piles of broken scrap and metal everywhere. Would you be able to guess how many cars existed after this carnage? Of course not!
TFN: Having only the LDL-C doesn't always give us an accurate picture since we don't know how the cholesterol is spread out.

Uhh...

BAD POKER FACE

TFN: Just think of it like traffic. The more cars (particles) the more risk of crashing into an artery wall

See how there are 5 people (cholesterol) before? We can take those same 5 people and have them fit one bigger car.

So if they all get into a bigger car (particle) despite their being the same amount of people (cholesterol) the risk is less? How does that work? Can't they still "crash?"

Yes of course! But having more smaller particles increases the concentration gradient that determines if they get into the artery wall. Think of it this way, are you more likely to have a traffic accident with less cars or more cars on the road?

So getting the regular cholesterol checkup is useless then?

TFN: Not at all! It can give your doctor an estimate on insulin resistant (IR) and other inferences on your health! For most healthy people the LDL-C value represents LDL-P well. However, for some conditions such as diabetes, LDL-C may not be as accurate as LDL-P!

Therefore, the most accurate determination of risk is by LDL-P count for certain people.
"Okay, then what does saturated fat have to do with all this then? They are always telling me to avoid it!"

TFN: Ah that requires a little bit more history...

At the time they discovered that eating saturated fats raised LDL-C and found some associations with heart disease

= increased LDL-C

Since people could only commonly measure cholesterol and not the particles originally, they arrived at HDL-C = good and LDL-C = bad which people still think of today:

Don't know what HDL or LDL is...but I was told it's a simple story of good and evil!

This led to the start of huge longitudinal studies like the Framingham heart study to gather more data

...except it failed to show any significance of saturated fat.

To the left is Ronald Krauss who is one of the spiritual successors of John Gofman mentioned earlier. Krauss is notable for contributions to science by discovering that IDLs become LDLs through hepatic lipase. He also pointed out LDLs came in the different sized particles like the Russian dolls we discussed for VLDLs shown earlier and relating them to heart disease.

On LDL-C and heart disease in these longitudinal studies Krauss saw: "If you look in the literature and just look at the average coronary patients...their LDL-cholesterol levels are often barely discernibly elevated compared to patients who do not have coronary disease."

- Good Calories Bad Calories, Gary Taubes

= more small LDL-P

less small LDL-P =

Instead, Krauss' own studies showed that more small LDL-P would go up on high carb diets and down on high saturated fats!
So even tho saturated fat raised the total amount of LDL-C, it offered it in less particle numbers by having it be distributed in larger LDL-P whereas the high carb diets offered less LDL-C but more particles by having higher amounts of it distributed in small LDL-P. Remember, "It's about the cars not the passengers!"

Oh MY GAWDZ! This means Steak for breakfast, lunch and dinna!

TFN: Well...in theory but...not quite...

WHAT!? But you just said saturated fat is less LDL-P!

TFN: Krauss recently did an experiment with beef for breakfast lunch and dinner and found subjects actually increased small LDL-P! What!? But you said he found saturated fat didn't lead to more LDL-P before!

TFN: The previous study had mixed meats whereas this one had more red beef meat than a normal person would eat in a day. They are looking more into it. Could be the iron.

JUST TELL ME WHAT THE IDEAL DIET IS THEN!

TFN: No. Looking for a diet that works for everyone is what caused these problems in the first place!

We are still working out the science and Lipidology is approaching a new golden age. by trying to assign a "national diet" or such we will run into problems since we still don't know everything!

This is what happened when Senator McGovern released his "Dietary guidelines for Americans" saying fat was bad. The science wasn't conclusive on that yet!

So what do I do then!?

Without conclusive Data, even Gofman remarked low fat diets could do more harm than good

TFN: Find a way of eating that works for you as an individual. Work with you provider and make sure they know about cholesterol particles or what the latest evidence is.
Here's the bigger picture. We need to constantly evaluate the science and evidence around us and update our practices to match them. Otherwise we'll just be using teaching and using outdated methods that may no longer be effective. This requires evaluating claims not just in the media, which may not critique studies with a sharp eye, but also the journals themselves. Things are constantly changing. Heck, next year maybe everything mentioned in this comic will be outdated. If so, it means we are still making progress.

-TheFatNurse
Apolipoprotein B (APOB or ApoB) are the primary apolipoproteins of chylomicrons and low-density lipoproteins (LDL - known commonly by the misnomer "bad cholesterol" when in reference to heart disease), which is responsible for carrying cholesterol to tissues. While it is unclear exactly what functional role APOB plays in LDL, it is the primary apolipoprotein component and is absolutely required for its formation.

Atherosclerosis (also known as arteriosclerotic vascular disease or ASVD) is a condition in which an artery wall thickens as a result of the accumulation of fatty materials such as cholesterol. It is a syndrome affecting arterial blood vessels, a chronic inflammatory response in the walls of arteries, caused largely by the accumulation of macrophage white blood cells and promoted by low-density lipoproteins.

Chylomicrons are lipoprotein particles that consist of triglycerides (85-92%), phospholipids (6-12%), cholesterol (1-3%) and proteins (1-2%). They transport dietary lipids from the intestines to other locations in the body. Chylomicrons are one of the five major groups of lipoproteins (chylomicrons, VLDL, IDL, LDL, HDL) that enable fats and cholesterol to move within the water-based solution of the bloodstream.

Concordance: similar with respect to one or more particular characters.

C-reactive protein (CRP) is a protein found in the blood, the levels of which rise in response to inflammation (i.e. C-reactive protein is an acute-phase protein). Its physiological role is to bind to phosphocholine expressed on the surface of dead or dying cells (and some types of bacteria) in order to activate the complement system via the C1Q complex.

Cytokines (Greek cyto-, cell; and -kinos, movement) are small cell-signaling protein molecules that are secreted by numerous cells and are a category of signaling molecules used extensively in intercellular communication.

Discordance: dissimilar with respect to one or more particular characters—compare concordant.

Intermediate-density lipoproteins (IDL) belong to the lipoprotein particle family and are formed from the degradation of very low-density lipoproteins. IDL is one of the five major groups of lipoproteins (chylomicrons, VLDL, IDL, LDL, HDL) that enable fats and cholesterol to move within the water-based solution of the bloodstream. Each native IDL particle consists of protein that encircles various fatty acids, enabling, as a water-soluble particle, these fatty acids to travel in the aqueous blood environment as part of the fat transport system within the body. Their size is, in general, 25 to 35 nm in diameter, and they contain primarily a range of triacylglycerols and cholesterol esters. They are cleared from the plasma into the liver by receptor-mediated endocytosis, or further degraded to form LDL particles.
Insulin resistance (IR) is a physiological condition where the natural hormone insulin becomes less effective at lowering blood sugars. The resulting increase in blood glucose may raise levels outside the normal range and cause adverse health effects.

**LDL-C:** low-density-lipoprotein cholesterol (passenger).

**LDL-P:** Low-density lipoprotein particle (Car).

Lp-PLA$_2$ is involved in the development of atherosclerosis. In human atherosclerotic lesions, 2 main sources of Lp-PLA$_2$ can be identified, including that which is brought into the intima bound to LDL (from the circulation), and that which is synthesized de novo by plaque inflammatory cells (macrophages, T cells, mast cells)." It is used as a marker for cardiac disease.

A meta-analysis involving a total of 79,036 participants in 32 prospective studies found that Lp-PLA$_2$ levels are positively correlated with increased risk of developing coronary heart disease and stroke.

**Lipoprotein(a)** (also called Lp(a)) is a lipoprotein subclass. Genetic studies and numerous epidemiologic studies have identified Lp(a) as a risk factor for atherosclerotic diseases such as coronary heart disease and stroke.

**Macrophages** function in both non-specific defense (innate immunity) as well as help initiate specific defense mechanisms (adaptive immunity) of vertebrate animals. Their role is to phagocytose (engulf and then digest) cellular debris and pathogens, either as stationary or as mobile cells.

**Monocytes** are a type of white blood cell and are part of the innate immune system of vertebrates including all mammals (including humans), birds, reptiles, and fish. Monocytes play multiple roles in immune function.

**Phosphocholine:** one of the binding targets of C-reactive protein (CRP).[3] Thus when a cell is damaged, CRP binds to phosphocholine beginning the recognition and phagocytotic immunologic response.

**Plasminogen:** Precursor to Plasmin.

**Plasmin** is an important enzyme present in blood that degrades many blood plasma proteins, most notably, fibrin clots. The degradation of fibrin is termed fibrinolysis.

**Triglycerides** are the main constituents of vegetable oil (typically more unsaturated) and animal fats (typically more saturated). In humans, triglycerides are a mechanism for storing unused calories, and their high concentration in blood correlates with the consumption of starchy and other high carbohydrate foods.
Very-low-density lipoprotein (VLDL) is a type of lipoprotein made by the liver. VLDL is one of the five major groups of lipoproteins (chylomicrons, VLDL, low-density lipoprotein, intermediate-density lipoprotein, high-density lipoprotein) that enable fats and cholesterol to move within the water-based solution of the bloodstream. VLDL is assembled in the liver from triglycerides, cholesterol, and apolipoproteins. VLDL is converted in the bloodstream to low-density lipoprotein (LDL). VLDL particles have a diameter of 30-80 nm. VLDL transports endogenous products, whereas chylomicrons transport exogenous (dietary) products.

***Definitions taken from Wikipedia***