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What about LDL?

As discussed in

THE CARNIVORE CODE

by Paul Saladino, M.D.

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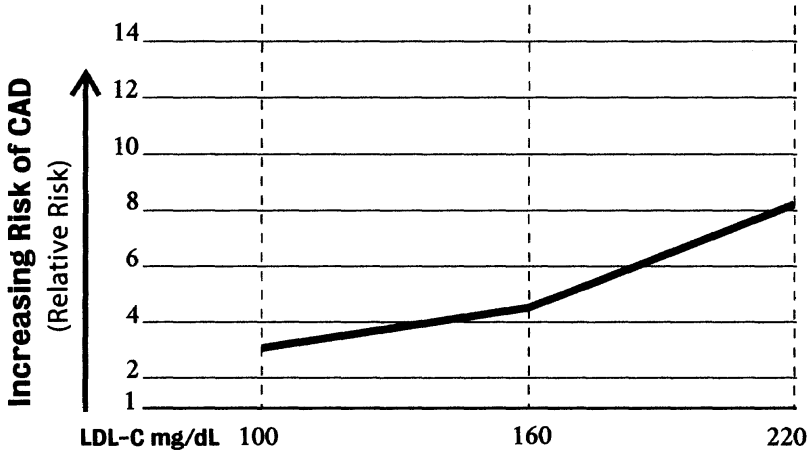
THE FRAMINGHAM STUDY
CAD RISK BY LDL

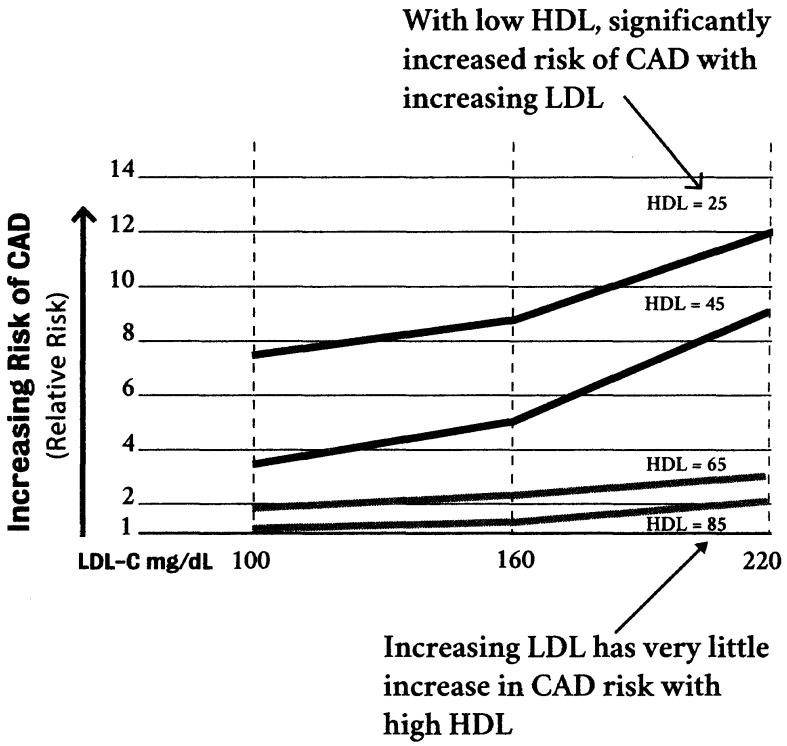


Gordon, T. et al., (1977). High density lipoprotein as a protective factor against coronary heart disease: The Framingham study. *The American Journal of Medicine*, 62(5): 707-714.

We can see why researchers might look at this and believe that there's a direct relationship between the amount of LDL in the blood and cardiovascular disease: the more total cholesterol and LDL, the more people from this study had cardiovascular events. But a very interesting thing happens to this graph when we separate all of the people studied into groups based on their levels of HDL.

Up to this point we've spoken about HDL only briefly when we discussed its role in reverse cholesterol transport. Another very interesting thing about HDL is that its level correlates directly with insulin sensitivity.[45, 46, 47] In those with insulin resistance, HDL levels fall and triglyceride levels rise, a change in blood parameters known as metabolic dyslipidemia.[48] Thus, those with the lowest levels of HDL are much more likely to have insulin resistance than those with higher levels of this lipoprotein.[49, 50] Looking at the graph that follows, it's immediately apparent that differences in HDL make a huge difference in cardiovascular disease risk. Keep in mind that this is exactly the same data from the Framingham Study depicted in the previous graph, but participants have been split into groups based on their HDL levels.

THE FRAMINGHAM STUDY
CAD RISK BY LDL AND HDL



What we quickly notice looking at this graph is that with low HDL (less than 45 milligrams per deciliter), there is a clear correlation between total cholesterol and heart disease, but in those with higher levels of HDL, *this correlation vanishes almost entirely.* What we see here is exactly what proponents of the response-to-retention hypothesis are missing. Atherosclerosis is about much more than just total cholesterol or LDL. **In those who are insulin sensitive, rising LDL levels do not correlate with increased rates of heart disease.**

Thinking about LDL levels within a vacuum is a critical mistake and a dangerously myopic perspective. When it comes to total cholesterol and LDL, context is everything! If we are insulin resistant, higher levels of LDL may very well contribute to plaque formation and progression, but if we are insulin sensitive, higher levels of LDL are not associated with increased atherosclerosis and are likely protective.

These findings help us explain the discordance in the epidemiology data regarding LDL and heart disease. It's not just about LDL, it's about insulin resistance. When thinking about heart disease risk and lipids, we must consider the overall health of the individual rather than looking only at LDL. And yet the vast majority of the time, if LDL is elevated, clinicians become overly focused on this, disregarding the HDL and triglycerides and very rarely taking into consideration other blood-markers reflective of insulin sensitivity, such as fasting insulin.

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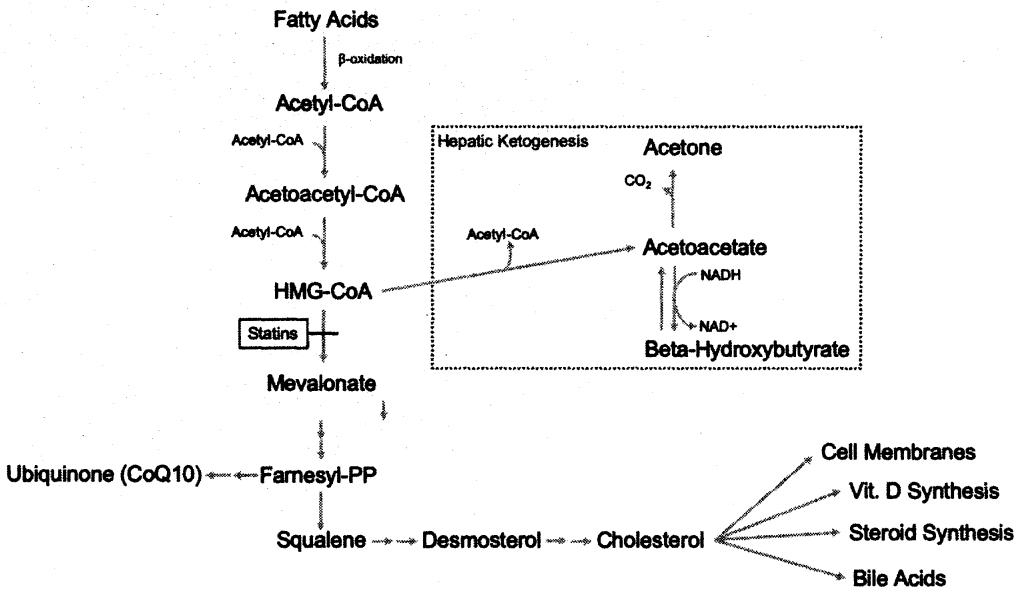
Why Does LDL Rise on a Ketogenic Diet?

When we think about LDL with an antiquated framework, elevations of this lipoprotein can look scary. As we've seen in this chapter, however, it's high time that we revise the LDL paradigm and stop incorrectly vilifying this crucial component of our healthy physiology. Elevated LDL is only a problem in the presence of insulin resistance, and if we don't have "sticky" LDL molecules and arterial walls, more is probably a good thing! Nevertheless, it's interesting to examine the mechanisms by which LDL rises during ketosis in order to explain this biological phenomenon and to allay further fears.



Examining the diagram of cholesterol synthesis above, which is known as the **mevalonate pathway**, we see that during ketosis, our body naturally breaks down fatty acid molecules into **Acetyl-CoA**. Acetyl-CoA can be used directly for energy in the mitochondria through the Krebs cycle. It can also be made into HMG-CoA and, subsequently, into cholesterol, or it can be made into ketones like **beta-hydroxybutyrate** (BHB). Mechanisms by which ketosis could be increasing cholesterol synthesis are complex and not fully understood, but it appears that since ketones and cholesterol share this common pathway, when more Acetyl-CoA is made into HMG-CoA for ketone synthesis, some of this could also form cholesterol. Strengthening this hypothesis is the observation that other cholesterol precursor molecules like **desmosterol** are also increased on a ketogenic diet.[94] Ketones are also known to provide the substrate required for the massive synthesis of cholesterol in the rapidly growing brains of infants and children through this synthesis pathway.[95]

Furthermore, both VLDL and LDL increase during fasting, which is most likely connected with this ketogenic physiology and a coupled increase in cholesterol synthesis.[96, 97] Throughout our evolution, it is certain that our ancestors experienced prolonged periods of calorie deficits or complete caloric deprivation when hunts were not successful and there were few plant fallback foods available. Does it make even an iota of sense that our bodies would have evolved a system in which a molecule that is *bad* for us, like so many claim LDL to be, would increase significantly during such times? No way! Intentional fasting is now practiced by millions around the globe with resulting weight loss, improvements in diabetes, and other metabolic derangements. Are people simultaneously getting healthier and developing atherosclerosis? Of course not! In this chapter, we've already talked in great detail about the hard science suggesting that LDL does not cause atherosclerosis, and from an evolutionary perspective, this possibility also appears illogical.

As we observed previously in our discussion of the Framingham Study, elevated LDL on its own does not appear to be contributing to the progression of atherosclerosis. Similarly, LDL that rises in the setting of ketogenic physiology is very unlikely to contribute to plaque progression and isn't something to be concerned about.

There's another situation of elevated LDL that we should touch on briefly here, known as **familial hypercholesterolemia** (FH). There are more than 2,000 polymorphisms in lipoprotein metabolism that can cause FH. Those with this condition often show levels of LDL that climb above 200 milligrams per deciliter. Proponents of the response-to-retention hypothesis will often point to genome-wide association studies or mendelian randomization studies of those with FH showing a correlation between LDL and heart disease. But there's a problem here. FH does not represent normal human physiology, and these polymorphisms often occur in conjunction with a propensity toward forming excess blood clots.[98, 99, 100, 101] Hmmm, let's think about this for a moment. Might this coexisting hypercoagulability confound things just a bit in these studies? I'd say so! We must not be fooled by this sort of data when thinking about the relationship between LDL and heart disease. For this reason, FH is clearly not a good model system for predicting the effect of elevated LDL in the setting of a ketogenic diet.

Should You Take a Statin for an Elevated LDL?

If we choose to begin a ketogenic diet like most versions of the carnivore diet, it's certainly possible that our LDL levels will rise. At this point in our journey, we know that this probably isn't a big deal and is likely

protective, but those thinking about lipids in the traditional way might believe that such a change would require the immediate need for a statin. It's important to address these medications briefly and to take a look at their limited pros and abundant cons.

At a fundamental level, we know that cholesterol is a precious molecule in our body and serves many, absolutely essential roles. Intuitively, wouldn't it seem that interrupting the synthesis of such a valuable compound would be a very bad idea? Surely we wouldn't want to do such a misguided thing. But this is exactly what millions of people throughout the world do every day when they take statin drugs. These pharmaceuticals significantly impair our body's ability to produce cholesterol by inhibiting the enzyme HMG-CoA reductase, one of the key steps in the mevalonate pathway.

As you can see from the previous graphic depicting this pathway, throwing a monkey wrench into the workings of this crucial enzyme won't just inhibit the formation of cholesterol, it will also inhibit everything else that is made downstream. This includes valuable compounds like CoQ10, which plays a vital role in proper functioning of mitochondria. We've talked about the mitochondria previously, but these cellular powerhouses are particularly dense in the heart and other muscles, and they play a critical role in insulin sensitivity. Wait, did I just suggest that by damaging mitochondria, statins could lead to insulin resistance? That's exactly what I am saying here! Depleting CoQ10 can lead to mitochondrial dysfunction, and not surprisingly, the use of statins has been associated with lower levels of this molecule, increased rates of heart failure, and diabetes.[102, 103] Use of statins has also been associated with increased rates of cognitive impairment because the synthesis of cholesterol needed by the brain is hindered by these drugs.[104] In large trials with these medications, rates of death by violent crime rise and mood worsens.[105, 106, 107, 108] As it turns out, depriving the brain of a vital nutrient like cholesterol makes people unhappy and angry.

Are these drugs really something that should be "in the water" as so many proponents of the response-to-retention theory have claimed?[109] In trials like Fourier and 4S, the use of statins decreases the incidence of heart attacks by a small percentage.[43, 110] I'm not saying that statins do not decrease cardiovascular mortality. They certainly have been shown to do this, but it's not happening by lowering LDL. As we've discussed earlier in this chapter, there is no dose-response relationship between LDL lowering with statins and improved outcomes, and many other drugs not in the statin class of medications that also lower LDL have repeatedly failed to show any benefits in terms of cardiovascular outcomes. Statins

have other pleiotropic effects, including being anti-inflammatory and immunomodulatory, which likely account for the small, but significant, improvements in cardiovascular endpoints observed in studies.

At the end of the day, I'm not a huge fan of statins. I don't believe that we should be focused on LDL lowering, but rather, correction of the insulin resistance and inflammation that are really driving atherosclerosis. The risks of these medications outweigh their benefits in most people, and diet and lifestyle modifications are a much more effective way to positively change the course of our cardiovascular health.

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135 references for Chapter 11 show in fine print on six full pages.

Chapter 11

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