KRESSER INSTITUTE
FOR FUNCTIONAL AND EVOLUTIONARY MEDICINE

Dyslipidemia - Part Two

Again, given the focus on blood chemistry as a screening tool, I'm going to mainly focus here on how to interpret the standard lipid panel and identify patients who need further workup, and then you can refer to the High Cholesterol Action Plan for more detailed information and the future advanced module I'm going to teach on dyslipidemia.

I also want to emphasize how to approach high cholesterol from a functional perspective. This is often not done even in the integrative and functional medicine setting. Since high LDL-P and high Lp(a)-P are the strongest risk factors, we need to examine what the underlying causes of elevations in these markers are.

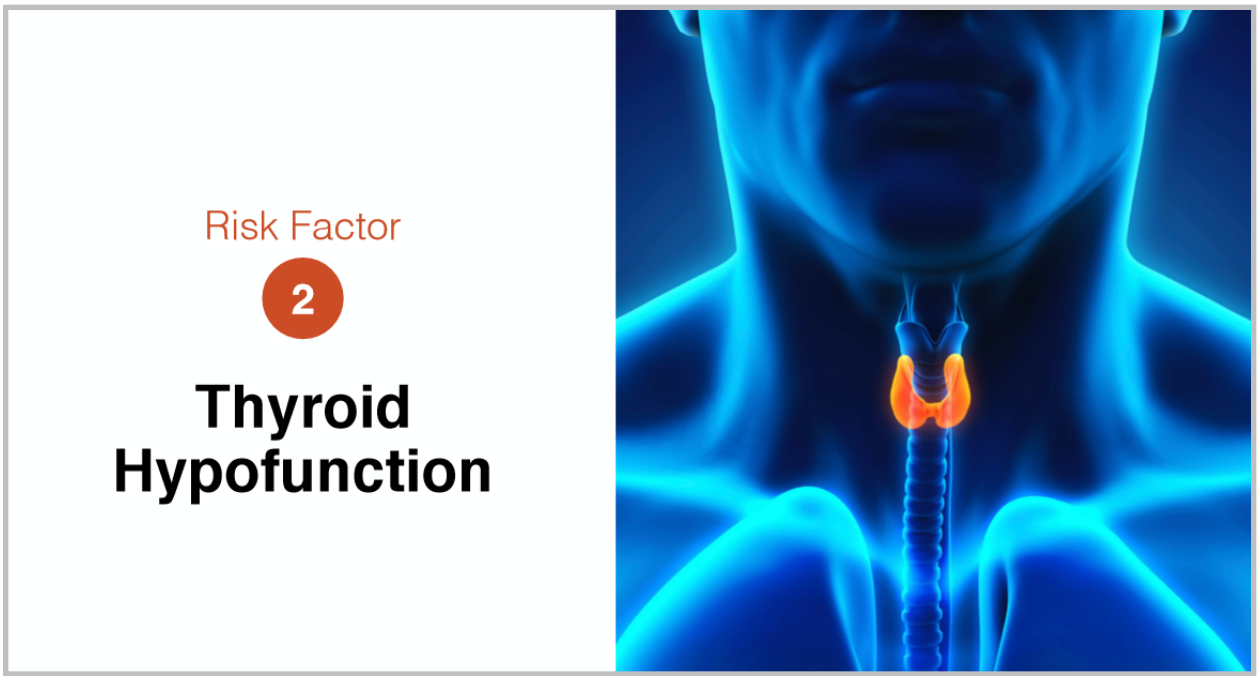
For Lp(a), the conventional thinking is that it is almost exclusively genetically determined. Unfortunately, there hasn't been much research on other potential causes of high Lp(a). I don't doubt that the genetic influence is strong, or even that genetics are the primary influence, but I have seen Lp(a) drop in many patients after addressing diet, lifestyle, and core pathologies, so I believe that there are modifiable risk factors that affect Lp(a), and we just don't have a lot of clarity on what they are at the moment.

For LDL-P, we can break down the causes into two categories: modifiable and nonmodifiable. Let's start with the modifiable risk factors for high LDL-P.

The first is insulin resistance, or metabolic syndrome. LDL particles don't just carry cholesterol. They also carry triglycerides, fat-soluble vitamins, and antioxidants, so you can think of LDL as a taxi service that delivers important nutrients to the cells and tissues of the body. Each LDL particle has a certain number of cholesterol molecules and a certain number of triglycerides, and as the number of triglycerides increases, the amount of cholesterol that they can carry decreases, so the liver will have to make more LDL particles to carry a given amount of cholesterol around the body. This person will end up with a higher number of LDL particles. If you consider two hypothetical people, both have an LDL cholesterol of 130 mg/dL, but one has high triglycerides, and the other has low triglycerides. The one with the high triglyceride level will need more LDL particles to transport that same amount of cholesterol around the body than the one with the low triglyceride level.

This highlights a crucial point. It's possible and not even uncommon to have normal or even low-normal total cholesterol but high LDL-P. These patients are often missed by conventional testing that only looks at total cholesterol and LDL but doesn't consider LDL particle number.

Numerous studies have found an association between increased LDL particle number and metabolic syndrome. One study measured apoB, which is kind of a surrogate marker for LDL-P, in a group of 1,400 young Finns with no established disease. The participants with the highest apoB levels were 2.8 times more likely to have metabolic syndrome than those with the lowest levels of apoB. A much larger study of over 300,000 men also found a strong association between LDL-P and metabolic syndrome and its components.



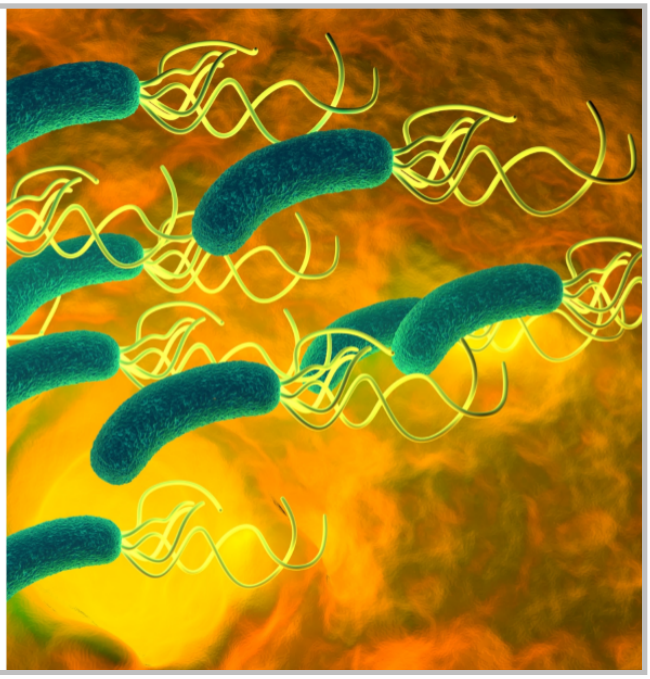
The next modifiable cause is thyroid hypofunction. Thyroid hormone has multiple effects on the regulation of lipid production, absorption, and metabolism. It stimulates the expression of HMG-CoA reductase, which is an enzyme in the liver involved in the production of cholesterol. Of course,

many of you know that that is the enzyme that statins inhibit, and that is how they reduce cholesterol. Thyroid hormone also increases the expression of LDL receptors on the surface of cells in the liver and other tissues. In hypothyroidism, the number of receptors for LDL on cells will be decreased. This leads to reduced clearance of LDL from the blood and thus higher LDL levels. Hypothyroidism may also lead to higher cholesterol by acting on Niemann-Pick C1-like protein, which plays a critical role in the intestinal absorption of cholesterol. Studies show that LDL particle number is higher even in subclinical hypothyroidism, which is high TSH with normal T4 and T3, and that LDL particle number will decrease after treatment with thyroid hormone. In fact, prior to the development of statins and other cholesterol-lowering drugs, some physicians used to use low doses of thyroid medication to lower cholesterol in patients, even when they had normal thyroid function or just subclinical hypothyroidism.

Risk Factor

3

Infection



The next modifiable cause is infection. Multiple studies have shown associations between bacterial infections such as Chlamydia pneumoniae, or Chlamydophila pneumoniae as it is called now, and H. pylori, which is the bacterium that causes duodenal ulcers, and then viral infections such as herpes and cytomegalovirus and elevated lipids. For example, H. pylori leads to elevated levels of total cholesterol, LDL cholesterol, Lp(a), apoB, or LDL-P and triglyceride concentrations, as well as decreased levels of HDL. Several mechanisms have been proposed to explain the association between infections and elevated blood lipids. Some evidence suggests that viral and bacterial infections directly alter lipid metabolism in infected cells, and other evidence suggests that lipids increase as a result of the body's attempt to fight off the infection. Other evidence suggests that LDL has antimicrobial properties and is directly involved in inactivating microbial pathogens. This has been confirmed by studies showing that mice with defective LDL receptors and thus very high levels of LDL are protected against infection by Gram-negative bacteria such as H. pylori.

Risk Factor

4

GI Pathology

The next modifiable cause is GI pathology. When the gut barrier fails, endotoxins such as lipopolysaccharide, or LPS, are produced by certain species of gut bacteria that enter the bloodstream and provoke an immune response. Part of that immune response involves LDL particles, which, as I mentioned on the last slide, can have an antimicrobial effect. A protein called LPS-binding protein, which circulates with LDL particles, has been shown to reduce the toxic properties of LPS by directly binding to it and removing it from the circulation. Studies have also shown significant increases in LPS-binding protein and thus LDL particles in cases of endotoxemia, a condition caused by large amounts of circulating endotoxins.

Also, we now have studies showing that the gut microbiota affects lipid metabolism. A disrupted gut biome can lead to dyslipidemia, and I have seen this clinically plenty of times. We've had patients come to me with high cholesterol or high LDL-P as their sole complaint. They don't have any symptoms. We test their gut. We find SIBO and/or other pathologies. We address those. LDL-P goes down by 30 or sometimes even 40 percent in some cases, and we'll look at a couple of these when we cover cases shortly.

Risk Factor

5

Environmental Toxicity

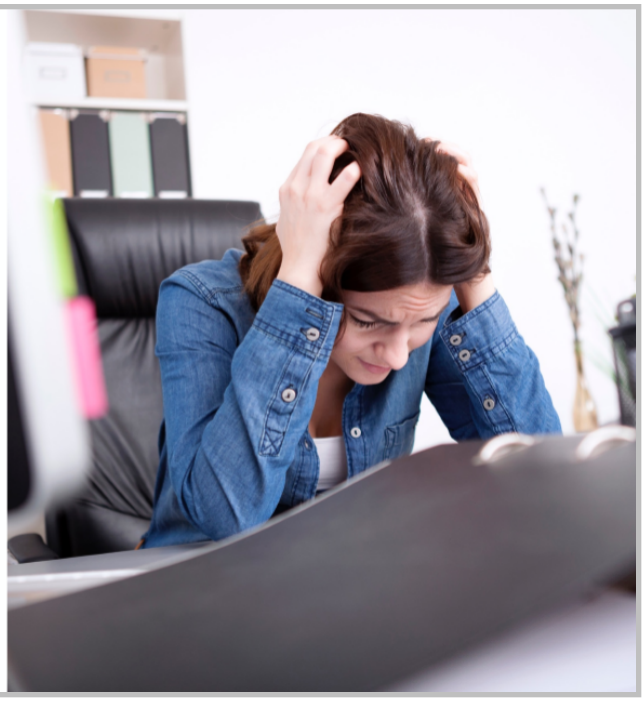
The next modifiable cause is environmental toxicity, and it's probably the least known and most poorly recognized even in the functional and integrative medicine communities. There is a strong association between mercury toxicity and metabolic syndrome, and we just reviewed how metabolic syndrome leads to elevated LDL-P and increased cardiovascular disease risk. Mercury toxicity has also been directly associated with dyslipidemia. Mercury has a number of vascular effects, including increased oxidative stress and inflammation, reduced oxidative defense, thrombosis, vascular smooth muscle dysfunction, endothelial dysfunction, dyslipidemia, and immune and mitochondrial dysfunction.

Another toxin associated with metabolic syndrome and dyslipidemia is bisphenol A. For example, BPA-treated rabbits showed insulin resistance, adipose accumulation, and fatty liver, and additionally, BPA exposure caused myocardial injury and enhanced the development of atherosclerosis in the aortic arch. It's possible and even probable that other toxins, including other metals, xenoestrogens, pesticides, phthalates, dioxins, PCBs, etc., can induce dyslipidemia with similar mechanisms.

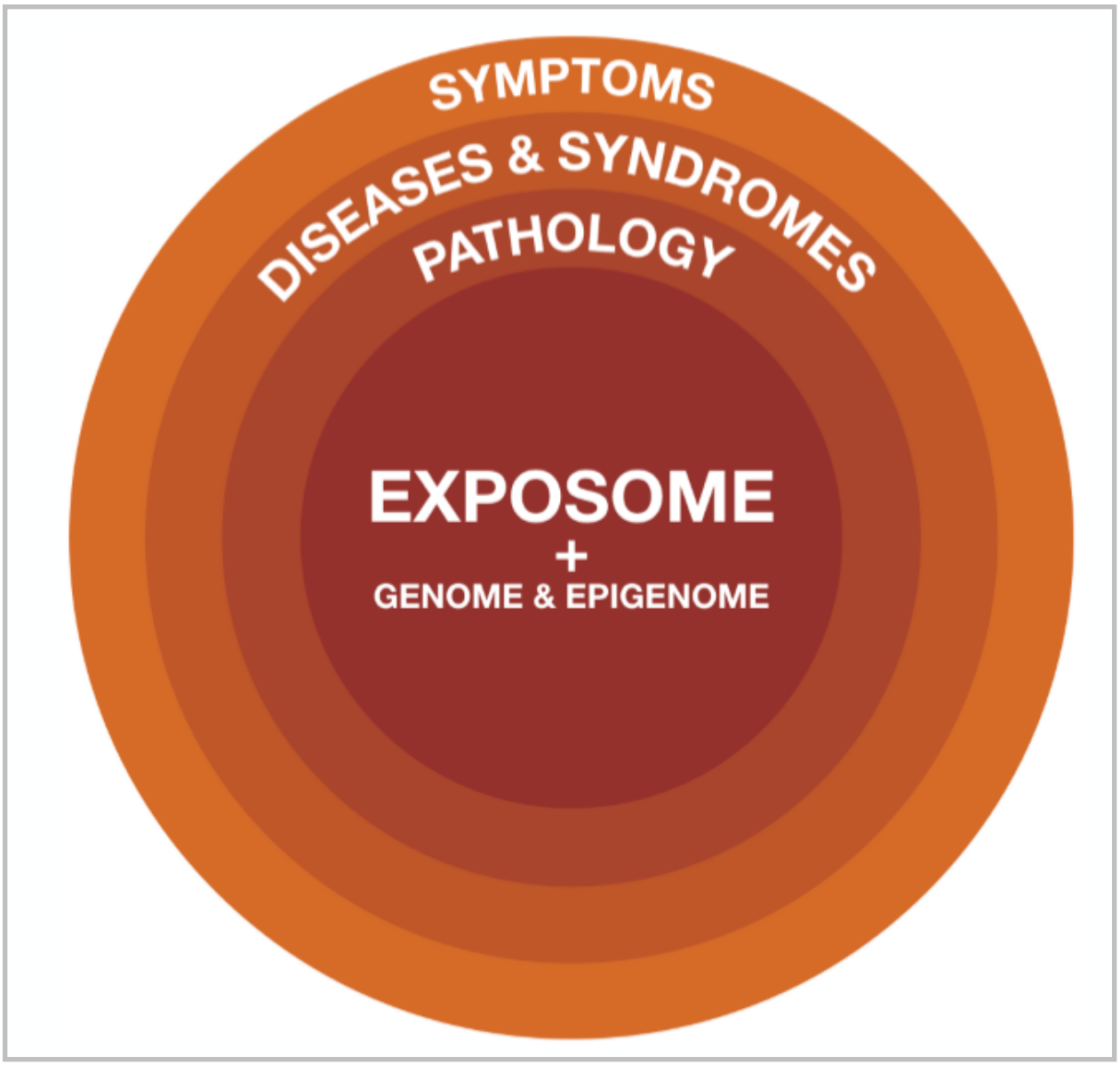
Risk Factor

6

HPA-D



The final modifiable cause of dyslipidemia to discuss is HPA axis dysfunction. There is less direct research on this, but studies on patients with Cushing's disease suggest that hypercortisolism leads to altered insulin secretion and insulin resistance, as well as increased lipogenesis and dyslipidemia. It's possible that more moderate hypercortisolism has similar albeit less dramatic effects on metabolic and cardiovascular health. It's difficult to parse out the relationship because we know that inflammation and glycemic dysregulation are the two triggers for HPA-D, and there is a bidirectional relationship. Anecdotally, I have seen improvements in lipid profiles after addressing HPA axis dysfunction, but they don't tend to be as significant as the improvements we get after addressing metabolic function and GI pathology.



Finally, a word on diet, lifestyle, and behavior. These primarily contribute to dyslipidemia via the mechanisms discussed on the last slide. For example, lack of physical activity and poor diet would lead to insulin resistance and metabolic syndrome, which in turn leads to dyslipidemia. Sleep deprivation and chronic stress lead to HPA axis dysfunction, which leads to insulin resistance and metabolic syndrome or hypothyroidism and dyslipidemia. Poor diet and chronic stress could lead to GI pathology, which leads to dyslipidemia. It should go without saying that you have to dial in diet and lifestyle as part of addressing dyslipidemia.

Let's move on to the non-modifiable causes of high LDL-P, and here we're primarily talking about genetics. Familial hypercholesterolemia, or FH, involves a mutation of a gene that codes for the LDL receptor or the gene that codes for the apolipoprotein B, or apoB protein. The LDL receptor sits on the outside of cells, and the LDL particle has to attach to the LDL receptor in order to

deliver the nutrients it is carrying and be removed from the circulation.

ApoB is the part of the LDL particle that binds to the receptor. If we use a door lock as an analogy, apoB would be the key, and the LDL receptor is the lock. They both need to be working properly for LDL to deliver its cargo and to be removed from the bloodstream.

Homozygous carriers of FH have two copies of a mutated gene, or the LDL receptor. This is very rare. It affects approximately one in 1 million people, and these people will develop extremely high total cholesterol levels, as high as 1,000 mg/dL during childhood, and they will usually die from severe atherosclerosis and heart disease before the age of 25. Heterozygous carriers are much more common, prevalence between 1 to 300 to 1 to 500, depending on the population, and they will have total cholesterol levels between 350 and maybe 500 or 600 along with very high LDL particle number.

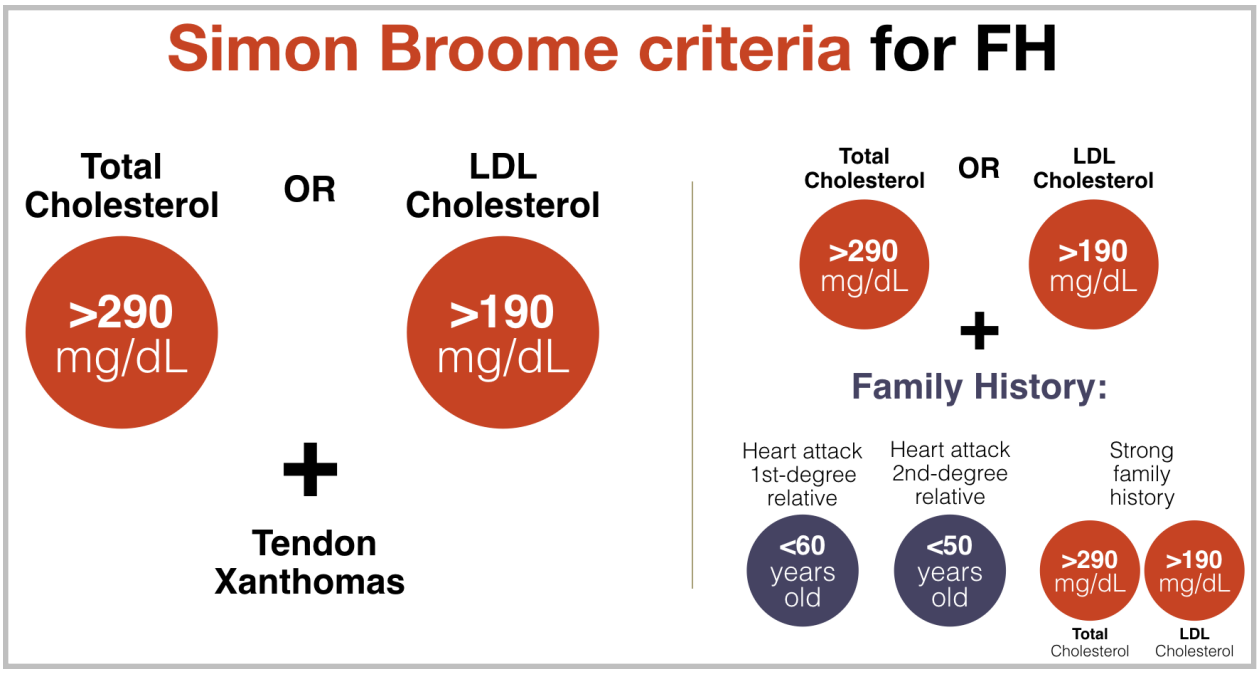
Size doesn't matter!
(At least not as much as number.)

A very important note here. People with FH have primarily large, buoyant LDL particles and yet are still at much higher risk for cardiovascular disease. At one point, it seemed that particle size was the most important factor. The idea was that small, dense LDL particles were more atherogenic, and large, buoyant LDL particles were protective and nothing to worry about. However, studies now have shown that particle size loses its significance when controlled for particle number. In other words, when you know the particle number, the size doesn't matter, and particle number always trumps particle size as a risk factor. This is evidenced by the fact that people with FH and large, buoyant LDL are still at threefold higher risk for cardiovascular disease.

Other genes such as apoE have been shown to affect LDL particle size and may affect particle number, but there is less research on this. ApoE has also been shown to affect dietary response to saturated fat, though the clinical relevance of this is questionable, and we'll talk more about that in the treatment section.

The question often arises clinically. Since genes aren't modifiable, should we do genetic testing for patients with high cholesterol? In the case of apoE, I do think it is important to know your genotype, but not primarily because of how it affects cholesterol levels, more because of the influence of apoE genotype on the risk of Alzheimer's and cognitive disorders. In the case of testing for mutations of the LDL receptor, that testing is available, but it is very expensive, about $1,000 at the time of this recording, and it's not covered by insurance because it doesn't change the treatment plan in the minds of the insurance companies. The apoB mutation can be found in the 23andMe raw data. However, only 1 to 5 percent of patients with FH have the apoB mutation, compared with 60 to 80 percent who have the LDL receptor mutation, so it's much less common, and a negative result doesn't really tell you anything.

The bigger question is whether genetic testing changes the treatment plan or outcome at all, and in my experience, it does not. There are many mutations that lead to FH that we can't even test for clinically, so a negative gene test doesn't rule out genetic causes. We're still ultimately looking at LDL-P and Lp(a)-P as the targets of treatment, so genes only matter insofar as they influence these targets. My approach has been to address underlying causes, and then if the numbers are still elevated, assume that the remaining influence is genetic.



In the absence of genetic tests, you can use the Simon Broome criteria to diagnose FH. The Broome criteria state that a definite diagnosis of FH can be made in an individual if two factors are present: total cholesterol is above 290 mg/dL or LDL cholesterol is above 190 mg/dL, and the individual has tendon xanthomas. Tendon xanthoma is a nodule on the tendon resulting from a buildup of cholesterol and other fats.

A possible diagnosis can be made with the same levels of total cholesterol and LDL cholesterol along with one of the following: a history of heart attack in a first-degree relative under 60 years of age, in a second-degree relative under 50 years of age, or a strong family history of total cholesterol above 290 mg/dL and LDL above 190 mg/dL.