What's the Best Predictor of Heart Disease?

Analysis by Dr. Joseph Mercola | January 18, 2024

STORY AT-A-GLANCE

> High total cholesterol and/or elevated low-density lipoprotein (LDL) cholesterol do not cause atherosclerosis

> Low levels of high-density lipoprotein (HDL) cholesterol are associated with both atherosclerosis and insulin resistance, and insulin resistance appears to be the foundational cause of heart disease. As such, the fasting insulin test is one of the best predictors of atherosclerosis

> Insulin resistance is primarily driven by excessive consumption of the omega-6 fat linoleic acid (LA). High LA intake is also associated with elevated levels of oxidized LDL — found in atherosclerosis plaque — further confirming this link

> One theory is that oxidized LDL protects your body from oxidative damage by sacrificing itself. If true, it may be beneficial to have higher, rather than lower, LDL levels

> The apoB test can also be helpful in assessing your atherosclerosis risk. As mentioned above, apoB is the primary carrier for LDL, and research over the past decade shows it's an accurate predictor of cardiovascular risk when apoB is high and LDL is normal

Is high total cholesterol and/or elevated low-density lipoprotein (LDL) cholesterol indicative of elevated heart disease risk? According to Dr. Paul Saladino, the answer is no. With regard to total cholesterol, as far back as 1977, with the publication of the Framingham Study,[1] no correlation between heart disease and total cholesterol could be found.

Low levels of high-density lipoprotein (HDL) cholesterol was associated with coronary heart disease, but not high LDLs or total cholesterol. However, as noted by Saladino, low HDL is also associated with insulin resistance, and he believes this is part of the confusion.

Saladino suspects that what has been blamed on LDL (atherosclerosis) is due to insulin resistance, i.e., metabolic dysfunction. Insulin resistance/metabolic dysfunction, in turn, is primarily driven by excessive consumption of the omega-6 fat linoleic acid (LA).

High LA intake also raises your levels of oxidized LDL, which are what you find in atherosclerosis plaque. In the video above, Saladino and Dr. Nadir Ali specifically discuss the role of oxidized LDL, and why it is not a direct cause of atherosclerosis, as commonly thought.

Summary of Available LDL Tests

But before I summarize Saladino's and Ali's discussion, let's take a look at the available LDL-related tests, as there's more to LDLs than the total amount.

- A regular LDL cholesterol blood test (LDL-C), which measures the total amount of LDL cholesterol in your blood

- A nuclear magnetic resonance lipoprofile (NMR lipoprofile) test, which measures the size of the LDL particles (LDL-P), which is thought to be more predictive of your cardiovascular risk, even if you have low total cholesterol[2]

- Oxidized LDL (oxLDL) test, which measures the level of LDLs that have been damaged by oxidation

- The apolipoprotein B (apoB) test, which measures the number of apoB particles in your blood. ApoB is a protein involved in the metabolism of lipids and the primary carrier for LDL. This test is a good predictor of cardiovascular risk, and does so far more accurately than the standard cholesterol panel

- Advanced lipid testing, which measures the amounts of large-buoyant LDLs (lbLDL) and small-dense LDLs (sdLDL), with the sdLDLs being associated with insulin

resistance and heart disease[3]

High LDL Does Not Cause Atherosclerosis

When it comes to LDL cholesterol, the most important factor is the level of oxidized LDL, as oxLDLs are primarily what you find in atherosclerosis plaque.[4] Unfortunately, most doctors will simply prescribe a statin drug or PCSK9 inhibitor if LDLs are high, to reduce the total LDL.

> **❝ A theory proposed by Dr. Nadir Ali is that oxidized LDL may protect your body from oxidative damage by sacrificing itself. If true, it may be beneficial to have higher LDL. ❞**

As noted by Ali in the short video above, this is a serious mistake. The primary question that needs to be asked is why is LDL oxidized in the first place, and how can you prevent that oxidation from taking place?

> *"Is the oxidized LDL a bad player?"* Ali asks, *"[or] is it there to protect us from oxidative injury? Rather than letting the important cells get oxidized, is the LDL sacrificing itself in protecting the body? Then, your whole paradigm changes ...*
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> *LDL is not a bad player — it's trying to protect us. What I need to figure out is how do I prevent this oxidative injury in the first place, and an argument that should surface is that, maybe I should have more LDL around so that oxidative injury can be ... prevented, rather than having less LDL? These are the kinds of fundamental questions that science should be asking."*

Oxidized LDL May Be a Protective Mechanism

Saladino agrees, saying that LDL "is probably a repository for oxidized phospholipids," much like lipoprotein(a) (Lp(a)). He cites research showing that the more polyunsaturated fats (PUFAs) you consume — such as LA — the higher your Lp(a) and oxidized LDL.

So, your LDL may in fact have a protective rather than injurious role. It may protect you from the harmful effects of LA and other PUFAs. What this means, then, is that high oxidized LDL may be a marker of high PUFA consumption, and it's the PUFAs, LA in particular, that are driving the atherosclerotic disease process.

The primary way to prevent atherosclerosis, then, is to radically reduce your LA intake by eliminating seed oils from your cooking, and avoiding processed foods (which are loaded with seed oils) and restaurant foods (as most are cooked in seed oils).

When it comes to measuring your oxLDL, the Boston Heart test called oxidized phospholipids on APO-B (OxPL/apoB) appears to be a better choice than the traditional oxLDL. The oxLDL tends to be inaccurate because it's just a proxy for APO-B and the LDL number, while the OxPL/apoB test gives you a truer measure of your oxidized LDLs.

The ApoB Test

Aside from oxLDL, the apoB test can also be helpful in assessing your atherosclerosis risk. As mentioned above, apoB is the primary carrier for LDL, and research over the past decade shows it's an accurate predictor of cardiovascular risk when apoB is high and LDL is normal. As reported by The Washington Post:[5]

> *"The standard cholesterol panel calculates the total quantity or concentration of 'bad' cholesterol or LDL in the blood, in milligrams per deciliter (technically, LDL-C). Because cholesterol is a fatty substance and thus not water-soluble, it must be carried around in little particles known as lipoproteins.*
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> *Testing for apoB, a protein on the outside of LDL-carrying particles, counts the number of these lipoprotein particles in the blood. In addition to LDL, it also*

captures other types of cholesterol such as IDL (intermediate-density lipoproteins) and VLDL (very low-density lipoproteins), which carry triglycerides.

Why is this important? As our understanding of heart disease improves, scientists are recognizing that apoB particles are more likely to become lodged in the arterial wall and cause it to thicken and eventually form atherosclerotic plaques. Thus, the total number of apoB particles matters more than the overall quantity of cholesterol that they carry.

In a majority of people, apoB and LDL-C track fairly closely, says Allan Sniderman, a professor of cardiology at McGill University in Montreal. But some people have a 'normal' amount of LDL-C, but a high concentration of apoB particles — a condition called 'discordance,' which means they are at greater risk."

sdLDL — Another Helpful Predictor of Atherosclerosis

Measuring your sdLDL-C can also be helpful, as explained by Dr. Eric Berg, a chiropractor, in the video above. The small-dense type of LDLs are indicative of inflammation inside your arteries, which is a hallmark of atherosclerosis. As noted by Berg, potential causes of this inflammation include:

- Seed oils

- Processed foods and junk foods

- Smoking

- Low vitamin E

- High glucose levels

Unfortunately, Berg lumps high-carb diets into these risk factors and recommends a ketogenic diet to avoid elevated sdLDL, but as I've explained in previous articles, high glucose levels are not necessarily a sign that you're eating too many (healthy) carbs.

In summary, when you consume significantly more than 30% fat, a metabolic switch called the Randle Cycle switches from burning glucose in your mitochondria to burning fat instead. As a result, glucose backs up into your bloodstream, thereby raising your blood sugar.

Glucose is actually a cleaner and far more efficient fuel than dietary fats, provided it's metabolized in your mitochondria and not through glycolysis. For a refresher, refer back to "Crucial Facts About Your Metabolism" and "Important Information About Low Carb, Cortisol and Glucose."

Atherosclerosis Is a Consequence of Metabolic Dysfunction

In the video directly above, Saladino debates LDL cholesterol with Dr. Mohammed Alo, a cardiologist and personal trainer. While Alo argues for the conventional LDL-atherosclerosis connection, Saladino highlights evidence showing that it's not LDL per se that is the cause, but rather insulin resistance in combination with high oxLDL, both of which are caused by high LA intake.

For this reason, Saladino believes one of the best assessments of your heart disease risk is a fasting insulin test, as your insulin sensitivity is such a foundational factor of your metabolic function. The OxPL/apoB test mentioned earlier would be a good complement.

If you have high fasting insulin, you are insulin resistant and hence have some degree of metabolic dysfunction (and, of course, mitochondrial dysfunction). Ideally, you want a fasting insulin level of 3 mcg/mL or less.

Most definitely, do not go by the "normal" ranges offered by labs in this case. Many will list levels as high as 24 mcg/mL as normal, when in fact that's a clear sign of serious insulin resistance and metabolic dysfunction.

If you're already eating a healthy diet, exercising, and all of your metabolic parameters look good, yet you have an insulin level of 7 or 8, the core culprit may be stress, because

when cortisol goes up, insulin rises with it. Cortisol release is a rescue mechanism to ensure you don't die from low blood sugar.

To assess whether stress is at play, keep an eye on your white blood cell count. Chronically depleted white blood cells are often a sign of chronic stress and high cortisol.

You can also get an AM cortisol test after fasting for 12 to 16 hours. You don't want to fast longer than that because, after 16 hours of fasting, cortisol will naturally start to rise. An ideal AM cortisol range is between 15 and 17. If your fasting AM cortisol is below 15, it's a sign you've become stuck in a long-term stress response.

High LA Intake Promotes Atherosclerosis

So, to summarize, Saladino argues that insulin resistance is the primary root cause for atherosclerosis — not elevated LDL or total cholesterol — and the primary driver of insulin resistance is excessive LA intake from seed oils. Lowering your LA intake is the foundational strategy to embrace.[6]

Low levels of high-density lipoprotein (HDL) is a proxy for insulin resistance, and if you have low HDL, then LDL tracks well with cardiovascular disease. But if you have normal HDL (65 to 85 mg/dL), then you typically have good insulin sensitivity and the correlation with LDL and atherosclerosis vanishes.

The Keto Trial Match Analysis[7] presented in mid-December 2023 (video below) confirms this, as they found no relationship between elevated LDL levels and arthrosclerosis plaque.

Other Tests to Assess Your Metabolic Health

In addition to the tests already mentioned, other blood tests that can help you assess your metabolic health include the following. Additional information about these and

other lab tests can be found in my interviews with Dr. Nasha Winters and Dr. Bryan Walsh.

- **Fasting glucose —** The ideal range is between 82 and 88 milligrams per deciliter (mg/dL), based on the available literature, while nonfasting glucose should ideally be between 82 and 130 mg/dL.

- **Gamma-glutamyl transferase (GGT)**, a powerful predictor of mortality, also should not be above 20 U/L. GGT is a liver enzyme involved in glutathione metabolism and the transport of amino acids and peptides.

   Not only will the GGT test tell you if you have liver damage, it can also be used as a screening marker for excess free iron and is a great indicator of your sudden cardiac death risk.

   GGT is highly interactive with iron. Excessive iron will tend to raise GGT, and when both your serum ferritin and GGT are high, you are at significantly increased risk of chronic health problems, because then you have a combination of free iron, which is highly toxic, and iron storage to keep that toxicity going.

   Cysteinylglycine is liberated from glutathione via GGT. That, in the presence of iron or copper, initiates the Fenton reaction. That's when you get massive oxidative stress.

- **The Intermountain health risk score** is a mortality risk score created based on the basic blood chemistry markers of tens of thousands of patients in a hospital setting, including complete blood count (CBC), sodium, potassium bicarbonate, mean platelet volume and other basics. Based on these markers, you end up with a 30-day, a one-year and a five-year mortality risk.

   A risk score calculator is freely available on the Intermountain website, where you can also find more information about this score.[8] Simply enter your variables and it will calculate your score for you.

- **Coronary artery calcium (CAC) scan** — This test provides images of your coronary arteries. Existing calcium deposits, an early sign of coronary artery disease, will show up on these images, and can therefore reveal your risk of heart disease before other warning signs become apparent.[9]

For even more information about cholesterol, and why high cholesterol and/or high LDL are not risk factors for heart disease, check out the video below by Dr. Ken Berry.

Sources and References

- [1] American Journal of Medicine May 1977; 62(5): 707-714
- [2] Front. Nuci. Med July 13, 2022; 2
- [3] Health Matters LDL Size
- [4] Mediators of Inflammation 2013; 2013: 714653
- [5] Washington Post January 8, 2024
- [6] Chem Phys Lipids January 1998; 91(1): 1-11
- [7] Citizens Science Foundation December 13, 2023
- [8] Intermountain Risk Scores
- [9] Hopkins Medicine CAC Test