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Low HDL Cholesterol and High Risk of Autoimmune Disease: Two Population-Based Cohort Studies Including 117,341 Individuals

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Guest: Dr. Borge Nordestgaard is Chief Physician in Clinical Biochemistry at Copenhagen University Hospital and Clinical Professor at the University of Copenhagen in Denmark.

Bob Barrett: This is a podcast from *Clinical Chemistry,* sponsored by the Department of Laboratory Medicine at Boston Children's Hospital. I am Bob Barrett.

High-density lipoprotein or HDL is one of the most important of the lipoproteins in most species and there is evidence that points towards a role of HDL in normal immune function. A paper appearing in the May 2019 issue of *Clinical Chemistry* tested the hypothesis that concentrations of HLD cholesterol are associated with risk of autoimmune disease.

That study from the Copenhagen General Population Study and the Copenhagen City Heart Study included over 100,000 individuals. We are pleased to have the senior author of that paper with us today, Dr. Borge Nordestgaard. He's Chief Physician in Clinical Biochemistry at Copenhagen University Hospital and Clinical Professor at the University of Copenhagen in Denmark.

And welcome back Dr. Nordestgaard. Most people know of HDL cholesterol, or high-density lipoprotein, but what exactly is HDL and why exactly do we have it?

Dr. Nordestgaard: HDL is a fat particle that also has some proteins in it that floats around in plasma. In most species, HDL is quantitatively the most important protein with the highest mass. But in humans, we also have other lipoprotein like LDL or remnants (00:01:18). It has lipids, it has cholesterol, it has a little bit of triglycerides, some phospholipids and then many different proteins. Most important called apolipoprotein A1, but then also many other proteins have importance for modulating lipids in plasma.

Potential function, it could be very important in the immune system, certainly as most all animals have it in very high quantity. You would think that through evolution, it might be important for survival. It also carries, for example, fat-soluble vitamins and essential amino acids.

Bob Barrett: It does seem of course that many researchers are interested in HDL. What are the novel findings of your study?

Dr. Nordestgaard: We have examined whether low HDL cholesterol is associated in a large perspective study with increased risk of autoimmune diseases. So, we studied what's called the Copenhagen General Population Study with 110,000 individuals from the Danish general population and followed them for eight years, and detected more than 4,000 cases of autoimmune diseases. Then as a control we had different study called Copenhagen City Heart Study with 10,000 individuals that we followed for 18 years, with 1100 autoimmune diseases developed prospectively. And we found very clear in both studies that a person that had low HDL cholesterol before development of disease, they have higher risk of autoimmune diseases during follow-up, up to 1.8 fold increase risk for those that had the lowest HDL, meaning, less than 39 milligram per deciliter or less than 1 millimole per liter.

Bob Barrett: How can we understand these findings mechanistically?

Dr. Nordestgaard: I don't know exactly how to understand it, but I can certainly speculate based on what's in the literature so far. So, I think it is likely that what's called dysfunctional HDL, or just low HDL per se, can modulate inflammatory and autoimmune processes. Certainly, it has been known for a long time that HDL is very important for transport of excess cellular cholesterol. And therefore, this could also be important for how cells work.

So, you can say that in support, many clinical studies where HDL has been involved or implicated in proper immune function, for example, via proliferation of hematopoietic stem cells in the bone marrow or by modulation of immune cell activity via interaction with receptors on the cell surfaces.

Bob Barrett: Have we recently learned other noble aspects of high or low concentrations of HDL?

Dr. Nordestgaard: Within the last few years, there's been a number of publications, and we have certainly from our group had two publications published within the last two years, in what's called the *European Heart Journal*, showing -- I would say surprisingly to me at least -- that the people with the highest HDL cholesterol, they had high risk of mortality so they died more, and you would have thought it would be the other way around.

And in another publication, the same individuals with highest HDL cholesterol, they had high risk of infectious disease. The ones with low risk, also had high mortality,

high infectious disease risk, but that probably comes together with what we know that low HDL also is a major cardiovascular risk factor.

Bob Barrett: Should these findings change the way we currently think about HDL?

Dr. Nordestgaard: I think so. I think that's been so much focus on the so-called reverse cholesterol transport, how HDL could take up cholesterol from peripheral tissues and bring it back to the liver for excretion. Certainly, this would not be a thing that would have been developed through evolution, I don't think so. Because it's much more likely that HDL could be important for something like infectious disease or immune function and now, also as we show here autoimmune diseases in particular because HDL is the most important lipoprotein in most species. So survival it can certainly be important for.

Bob Barrett: Well finally, Dr. Nordestgaard, we've always heard that LDL, or low-density lipoprotein, is the bad lipoprotein and HDL is the good one. Should we still believe that's true?

Dr. Nordestgaard: No, we have to take that out of how we believe in it. I see there's four different lipoprotein classes. There's HDL, there's LDL, there's remnants, or some call it triglycerides, which are proteins, and then there's (00:05:38). HDL, from all the evidence we have now, do not seem to be important in predicting cardiovascular disease or probably not on reverse cholesterol transport, certainly not from the arterial wall, maybe from other tissues.

So HDL, the "good lipoprotein," they don't call it that anymore. LDL is still the bad lipoprotein, no doubt about that. It causes atherosclerosis, myocardial infarction, and other cardiovascular disease end points. But then we have the remnants. They seem to be as or maybe even more important than LDL in causing atherosclerosis and cardiovascular disease. And finally, the very genetically determined lipoprotein lipoprotein(a) that is like LDL, but has a different protein called apolipoprotein (00:06:23) and that might be important in causing or promoting thrombosis if there is a plaque rupture leading to more myocardial infarction and stroke.

So, the LDL remnants, they are all very bad lipoproteins, but don't call HDL, the good one anymore. If anything, maybe the innocent one for cardiovascular disease, but important for other diseases.

Bob Barrett: That was Dr. Borge Nordestgaard, Chief Physician in Clinical Biochemistry at Copenhagen University Hospital and a Clinical Professor at the University of Copenhagen. He's

been our guest in this podcast on high-density lipid protein cholesterol and the risk of autoimmune disease. His population-based study on that top appears in the May 2019 issue of *Clinical Chemistry*.

I'm Bob Barrett. Thanks for listening.