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Type III Hyperlipoproteinemia: The Forgotten, Disregarded, Neglected, Overlooked, Ignored but Highly Atherogenic, and Highly Treatable Dyslipoproteinemia

Article:
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Guest: Dr. Allan Sniderman is the Edwards Professor of Cardiology at McGill University in Montreal, Quebec, Canada.

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.

Cardiovascular risk is so high in type III hyperlipoproteinemia that is typically a "treat immediately on diagnosis" disorder. In the February 2019 issue of *Clinical Chemistry*, a paper presented the advantages of a non-high density lipoprotein cholesterol ratio with apolipoprotein B as a diagnostic tool for type III hyperlipoproteinemia. In the same issue, an accompanying editorial entitled "Type III Hyperlipoproteinemia: The Forgotten, Disregarded, Neglected, Overlooked, Ignored but Highly Atherogenic, and Highly Treatable Dyslipo-proteinemia" was also published. The author of that article is Dr. Allan Sniderman, the Edwards Professor of Cardiology at McGill University in Montreal, Quebec, Canada, and he is our guest in this podcast. So, Dr. Sniderman, we will get basic first, what is type III hyperlipoproteinemia?

Dr. Allan Sniderman: Type III hyperlipoproteinemia is a highly atherogenic dyslipoproteinemia. It is characterized generally by elevation of both cholesterol and triglyceride. Type III appears in mid-life. It is often associated with abdominal obesity or diabetes, and the challenge is to recognize which patients with high triglycerides or cholesterol have type III and which don't, because type III is so dangerous that when the diagnosis is made, those patients should be treated just like patients with familial hypercholesterolemia are treated on diagnosis.

Bob Barrett: So, let us get into this. What is so special about type III hyperlipoproteinemia.

Dr. Allan Sniderman: Type III is so special because it is so dangerous. It can't be diagnosed using the conventional lipid panel. With only cholesterol and triglycerides and LDL cholesterol and non-HDL cholesterol and HDL cholesterol, you cannot identify these patients with type III hyperlipoproteinemia.

The problem in type III, the specific abnormality in type III hyperlipoproteinemia, is an accumulation of partially

metabolized chylomicron particles. Those are the particles that transport dietary triglycerides from the intestine to adipose tissue in the liver, and also the accumulation of the VLDL remnant particles that normally, they're not as quickly metabolized as chylomicron particles, but the triglyceride is generally relatively rapidly removed within a few hours and the particles are either removed or converted to LDL particles.

In type III for reasons that are still not well understood, the interaction of the partially-metabolized chylomicron or VLDL particle with the liver is defective and the particles are not removed the way they should be. So, they accumulate in plasma and they become much richer in cholesterol than they should be. So that you have got these remnant-particles which are markedly increased in cholesterol accumulating in plasma and they are highly atherogenic and that's the problem, you've got a patient with a highly atherogenic disorder, which by the way is relatively easy to treat, but can't be diagnosed using the conventional lipid approach and so, we're missing most of these patients, they're not being identified, they are not being treated, their disease is not being prevented.

Bob Barrett: And well, the obvious next question is, what causes this?

Dr. Allan Sniderman: Well, I wish that we knew, we know that the removal process is defective or the conversion process of VLDL to LDL, that is defective and in some way it involves apo E, which is one of the apoproteins, the proteins that are found on the VLDL and chylomicron particles, and the apo E comes in, there are three alleles, and when people are homozygous for apo E2E2, that allele, they're susceptible to type III.

But measuring apo E2E2, identifying an E2E2 homozygote, isn't insufficient to make the diagnosis because only a small proportion of those actually developed type III hyperlipoproteinemia. So, in the parlance, this is a two-step disorder. We know one of the steps and it involves apo E, but what the other steps are, we are not sure. The clinical core associates are abdominal obesity and type II diabetes, but in what specific way they interact is not known. So, the challenge is to further characterize what is wrong at a scientific level, but the clinical challenge is to diagnose a disorder.

Originally when the disorder was recognized, diagnosis was based on ultracentrifugation or paper electrophoresis and those techniques aren't available now, even in highly specialized lipid clinics. So, for the most part, tragically, these patients are going unrecognized. That doesn't have to be case anymore.

Bob Barrett: Does that mean that typically-used laboratory tests are not helpful in the diagnosis of type III hyperlipoproteinemia?

Dr. Allan Sniderman: It absolutely does. In order to diagnose type III, one has to measure apoB in addition to total cholesterol and plasma triglyceride. In fact, just measuring total cholesterol and apoB and looking at the ratio of those two, will get you a long way home. But in our work, we have included in our apoB diagnostic algorithm, total cholesterol, triglyceride, apoB, and that will give you the diagnosis, not just of type III, but of all the other important apoB dyslipoproteinemias.

ApoB is easy to measure, the measurement is standardized, it's not expensive, it can be done in any clinical chemistry laboratory, and it has multiple uses other than type III, but type III is what we're presently discussing today.

Bob Barrett: Well, then, how can you accurately diagnose type III hyperlipoprotonemia?

Dr. Allan Sniderman: Well, the hallmark from a lipoprotein particle characterization point of view is the massive accumulation of these markedly cholesterol-enriched particles. Normally, for every one chylomicron particle or chylomicron plus chylomicron remnant particle, there would be about 10 VLDL particles and for every VLDL particle, there would be about 9 LDL particles. So, normally, chylomicrons and remnants make up only a tiny fraction of the apoB particles.

In this disorder, they make up over half of the total VLDL particles and the number is 40 to 60 times normal, plus the VLDL particles, because of the defect, don't get normally converted to LDL particles. So, LDL particle number is low. So, this is the only atherogenic apoB dyslipoproteinemia in which apoB is not elevated. In type III, apoB is characteristically normal or even low. That is how the algorithm can recognize these patients. They have a high total cholesterol apoB ratio, the absolute level of apoB is low, and the level of the ratio of triglyceride to apoB is high, but not as high as in patients who have accumulations of intact chylomicron particles. So, from a laboratory processing and diagnostic view point, it all is very simple, so long as apoB is included in the standard mix of laboratory tests to diagnose dyslipoproteinemia.

Bob Barrett: Once we have the diagnosis, how do you treat type III hyperlipoproteinemia?

Dr. Allan Sniderman: With a combination of diet, a low-fat diet but not an excessively high carb diet, plus fibrates and statins will reverse the lipid abnormalities and the cholesterol and triglycerides will go down, the apoB may even go up a little bit because the abnormal particles have been converted.

The abnormal VLDL particles can now be converted to normal LDL particles, but the apoB will be normal or low and everything will be fine.

Type III in a way should be thought of as a forgotten country cousin of familial hypercholesterolemia. Everybody knows about familial hypercholesterolemia, that cholesterol levels are massively elevated, they are at extremely high cardiovascular risk, But the genetic forms of the familial hypercholesterolemia—they're challenging to treat. Type III is just as common, if not more common, than familial hypercholesterolemia, and it is easy to treat.

That's why it's so disturbing that the diagnosis isn't made, and the diagnosis isn't made because apoB isn't measured, because these patients can be identified and treated, and their treatment shouldn't be based on what their ten-year cardiovascular risk is. The treatment should be based on diagnosis of type III. It's sufficient to justify the risk, the clinical risk is so high that therapy is justified on diagnosis.

Bob Barrett: Well, finally, Dr. Sniderman, why do you believe that type III hyperlipoproteinemia has become what you call an orphan disorder?

Dr. Allan Sniderman: I'm not sure. I'm not sure why. I think there hasn't been enough diversity of viewpoint in the lipid world and I don't think that clinical chemists have participated as fully in contributing your expertise to the issue of what should be measured and why. I believe that apoB should be a standard measurement for every patient because I believe the evidence is now irrefutable that apoB is a more accurate measure of cardiovascular risk than LDL cholesterol, non-HDL cholesterol, total cholesterol, or triglyceride.

In fact, you don't even need to measure those things. You can just measure apoB if you're doing routine care. There has been a, to me, inexplicable reluctance to examine why in a system in which lipids are transported within lipoprotein particles, we have restricted our measurement to the lipids and we haven't measured the particles, which is exactly what apoB does. These are not evidence-based decisions. They've been driven unfortunately, I think, by guidelines which should become codified and not followed as rapidly as they should. The evidence that we can improve care, the laboratory measurement of LDL cholesterol is far from ideal. Why LDL cholesterol should be the gold standard in care I cannot fathom, and it's unfortunate because it means that patients are not receiving the quality of care they could, if we were using the standards of measurement that should be available from a routine clinical chemistry laboratory.

Bob Barrett: That was Dr. Allan Sniderman, the Edwards Professor of Cardiology at McGill University in Montreal, Quebec, Canada. He has been our guest in this podcast on Type III Hyperlipoproteinemia. His editorial on the disorder appears in the February 2019 issue of *Clinical Chemistry*. I'm Bob Barrett. Thanks for listening.