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Cardiometabolic Considerations in Familial Chylomicronemia Syndrome

**Announcer:**
You're listening to *On the Frontlines of Familial Chylomicronemia Syndrome* on ReachMD. And now, here's your host, Dr. Steve Jackson.

**Dr. Jackson:**
Welcome to *On the Frontlines of Familial Chylomicronemia Syndrome* on ReachMD. I'm Dr. Steve Jackson, and today I'm joined by Dr. Robert Eckel to discuss the cardiometabolic effects of familial chylomicronemia syndrome, or FCS for short. Dr. Eckel is a Professor of Medicine Emeritus at the University of Colorado Anschutz Medical Campus, with appointments in endocrinology, metabolism and diabetes, and cardiology. Dr. Eckel, thanks so much for being here today.

**Dr. Eckel:**
It's good to be with you, Steve. Thanks for inviting me.

**Dr. Jackson:**
Let's start with the basics, Dr. Eckel. How does FCS disrupt normal lipid metabolism, and what does that mean for a patient's overall cardiometabolic health?

**Dr. Eckel:**
Well, to begin with, FCS is not a common disorder. It's a genetically driven disease of an absence of lipoprotein lipase, a key enzyme in triglyceride clearance from plasma. And typically, it's LPL—the enzyme itself—that's deficient, but sometimes, it's the regulators of lipoprotein lipase that are deficient. But in the absence of lipoprotein lipase, basically, you enter a space that we call zero-order kinetics. That means there's no enzyme there that's rate limiting and clearing triglycerides from the plasma compartment.

Now, triglyceride-rich lipoproteins occur in two forms. One is VLDL: very low-density lipoproteins, made by the liver. And the second are chylomicrons, which are made by the intestine. And chylomicrons are generated by the ingestion of dietary fat.

So when you have no lipoprotein lipase… We know that after dietary fat ingestion—about three to four hours after we eat—the triglycerides are peaking in the plasma, because the chylomicrons take some time to enter the plasma compartment. They're slowly absorbed through the intestine and developed in the plasma through generally slow absorption through the lactates of the lymphatic system, and they don't peak for three to four hours after ingestion.

Now, when lipoprotein lipase is absent, those triglycerides are not rapidly cleared. And the evidence is, if you were to inject chylomicrons into the plasma compartment, lipoprotein lipase clears those within 15 to 20 minutes. So the idea is that having no enzyme when dietary fat is being ingested ultimately results in severe hypertriglyceridemia.

Now, VLDL also contributes to that, because whether you're fasted or fed, VLDL levels create levels of triglycerides in the plasma, and those are also not clear. But the major concern is the chylomicrons when they're not adequately metabolized by lipoprotein lipase absence, and therefore severe hypertriglyceridemia is the common result of FCS.

Now, it's important to point out that people develop severe hypertriglyceridemia from other etiologies, and FCS is rare compared to other forms of severe hypertriglyceridemia. So this is an important step for the clinicians to consider: distinguishing multifactorial severe hypertriglyceridemia from people who have FCS, LPL deficiency, or defects in LPL regulation.

**Dr. Jackson:**

With that in mind, what cardiometabolic consequences are most clinically relevant in FCS and how do they differ from the more common dyslipidemias?

**Dr. Eckel:**
Well, FCS results in severe hypertriglyceridemia, and the consequences of that are not atherosclerotic cardiovascular disease, which we think of when triglycerides are more moderately elevated. But now the major clinical concern is that of acute pancreatitis. So acute pancreatitis occurs much more often in patients with FCS than it does in people with multifactorial severe hypertriglyceridemia, because in FCS, the treatments have been not very favorably in existence until very recently. And I think we'll turn to that in the near future.

But nevertheless, I think the cardiometabolic consequences are mostly, again, not in the vascular system, but in the acute pancreatitis outcome that's so severe and can be fatal under some circumstances.

**Dr. Jackson:**
Now, given those complexities, how do you approach risk stratification and monitoring in patients with FCS in routine clinical practice?

**Dr. Eckel:**
Well, I think if you see a patient with severe hypertriglyceridemia who's typically younger, thin, and not overweight or obese, in those types of patients, I think we might think about genetically screening for LPL deficiency or other genes that relate to LPL regulation. So I'm going to have the clinician put the thinking cap on when we are seeing that type of a patient, rather than the standard kind of patient with multifactorial severe hypertriglyceridemia, who may be patients who have insulin resistance, they may be obese and/or have type two diabetes, they may be on medications that make triglyceride production by the liver increased, et cetera.

But ultimately, the risk for pancreatitis is there for both patients. But because FCS is much more difficult to manage—because lipoprotein lipase is absent and ultimately correcting secondary factors that lead to hypertriglyceridemia—it's important for that patient that I just described to have genetic screening to define FCS from multifactorial severe hypertriglyceridemia.

**Dr. Jackson:**
For those just tuning in, you're listening to *On the Frontlines of Familial Chylomicronemia Syndrome* on ReachMD, and I'm Dr. Steve Jackson. I'm speaking with Dr. Robert Eckel about cardiometabolic risk in familial chylomicronemia syndrome.

So, Dr. Eckel, let's turn our attention to management now. Lifestyle modification has long been the cornerstone of FCS care. What does an effective dietary and lifestyle strategy look like today, and where do patients tend to struggle the most?

**Dr. Eckel:**
Well, see, that's a great question. I think historically in my fellowship years in Seattle, and then more recently in my decades of work at the University of Colorado Hospital, ultimately, I've seen a reasonably large number of patients with FCS.

Again, this is not a common disorder. In patients with FCS—and the same is true for patients with multifactorial severe hypertriglyceridemia—the lifestyle management needs to be strict dietary fat reduction. So I think, ultimately, as we continue to maintain dietary fat, chylomicrons continue to be produced, and ultimately, that severe hypertriglyceridemia is not sufficiently relieved by continuing to ingest dietary fat.

So typically, the recommendations that are published and up to date by guidelines of multiple organizations are suggesting a 10 to 15 percent dietary fat. My practice has been to reduce dietary fat much more extremely, to 5 percent of total calories for, maybe, three days, and have the triglycerides remeasured to see how quickly triglycerides fall.

Now, keep in mind, with multifactorial severe hypertriglyceridemia, we want to correct secondary factors, such as weight reduction, removing drugs that may result in hypertriglyceridemia, and controlling diabetes better. And, ultimately, when triglycerides get down to a level where drugs work—the usual triglyceride-lowering drugs—that's a success story that may require less dietary fat restriction for a prolonged period of time.

So measuring these triglycerides every three days or so gives me an idea of whether the patient's following the dietary recommendations. And in general, I think as a clinician, we expected a 20 to 25 percent fall in triglycerides over three days of extreme dietary fat restriction.

Now, most patients with FCS or other forms of severe hypertriglyceridemia cannot tolerate 5 percent dietary fat for very long, but for FCS, once we get patients down under, I would say, 1,500 to 1,000, then I think we're feeling more comfortable about the risk for developing acute pancreatitis.

So this is an important step, because until recently, we haven't had any pharmacological therapy that's been useful, and the usual

treatments for hypertriglyceridemia, which are fibrates, high-dose statins, and other drugs like niacin that are more historically utilized don't work in people with FCS.

So we have to realize that lifestyle modification with extreme dietary fat restriction is the only way to get patients under a level of triglycerides where, in fact, the risk for acute pancreatitis is much higher.

**Dr. Jackson:**
And with that being said, how are emerging pharmacologic therapies changing the treatment landscape for FCS, particularly in addressing both triglyceride levels and the broader metabolic outcomes?

**Dr. Eckel:**
Well, I think we're entering into a new paradigm of therapeutic options with several drugs that have been approved now to treat patients with severe hypertriglyceridemia. These drugs include olezarsen and plozasiran, and these drugs now are capable of modifying lipid and lipoprotein metabolism in the absence of lipoprotein lipase.

These drugs inhibit the production of Apo-C3, which is a protein that's part of the chylomicron composition and the LDL composition, which when modified, favorably affects triglyceride metabolism by allowing the liver to take up some of the particles that ultimately were not acted upon by lipoprotein lipase—so-called remnants that can result in triglyceride lowering.

Now, I think an important qualification needs to be made here. The question I have scientifically, and also as a clinician, is, if lipoprotein lipase isn't present, and that's the rate-limiting enzyme to lower triglycerides that are dietarily induced or produced under fasting conditions, how are remnants being generated?

And this is still somewhat controversial in terms of what other enzymes are important in this clearance, but nevertheless, the work that's been done with these agents has shown pretty clearly that these particles can be cleared effectively by inhibiting Apo-C3 production. Now, historically, Apo-C3 has been thought to be an inhibitor of lipoprotein lipase, but if there's no lipoprotein lipase there, or proteins that are used to regulate lipoprotein lipase are absent, then how does a drug that lowers Apo-C3 work, if we thought that that Apo-C3 related to an inhibition of lipoprotein lipase?

So I think in that particular situation, the work that's been done looking at remnant clearance is an important strategy to lower triglycerides, and we're using these newer agents in a way that can reduce triglyceride levels to levels may be putting a patient at less risk for acute pancreatitis—the major outcome that we're concerned about in patients with FCS.

**Dr. Jackson:**
Before we wrap up our discussion, Dr. Eckel, what are the biggest gaps in our understanding of cardiometabolic risk in FCS and what should clinicians keep in mind as they manage it over time?

**Dr. Eckel:**
Well, I think I mentioned a gap, which is that I think the understanding of how remnants are cleared when lipoprotein lipase or its regulators are not present is important. There must be other enzyme systems that I think scientifically need to be better studied to understand this better.

And is it possible that the drugs that are now available that inhibit the production of Apo-C3 work by mechanisms that ultimately relate to the clearance of larger particles, or maybe smaller particles that may depend on LPL less importantly, to be cleared by the liver through this remnant-related pathway? I think this is a major question that exists in this space.

I think another question that exists in patients with FCS is, how often do people who are screened for LPL deficiency actually have LPL deficiency when we are thinking of FCS? And I think this is another important question. While we use predictors of FCS versus multifactorial severe hypertriglyceridemia, they're useful about two-thirds or three-fourths of the time without genetic confirmation.

So if we use these platforms of predictors for FCS versus multifactorial, and we do not do genetic confirmation, how accurate are they in allowing a clinician to assume that patient has FCS versus other forms, which are much more common, of severe hypertriglyceridemia?

So I think these are a couple of questions that need to be addressed scientifically, which may have clinical implications.

**Dr. Jackson:**
With those key takeaways in mind, I want to thank my guest, Dr. Robert Eckel, for joining me to unpack cardiometabolic considerations in familial chylomicronemia syndrome management. Dr. Eckel, it was great having you on the program.

**Dr. Eckel:**
Thank you, Steve, for inviting me.

**Announcer:**
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