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Clinical Lipidology Roundtable Discussion

Severe hypertriglyceridemia†

W. Virgil Brown, MD*, John D. Brunzell, MD, Robert H. Eckel, MD, Neil J. Stone, MD, MACP, FNLA

Editor–in–Chief, The Journal of Clinical Lipidology, Charles Howard Candler Professor of Internal Medicine Emeritus, Emory University School of Medicine Emeritus, 1670 Clairmont Road, Atlanta, GA 30033, USA (Dr. Brown); Professor Emeritus of Medicine (active), Department of Medicine, University of Washington, Seattle, WA, USA (Dr. Brunzell); Professor of Medicine, Division of Endocrinology, Metabolism and Diabetes, Division of Cardiology, Professor of Physiology and Biophysics, Charles A. Boettcher II Chair in Atherosclerosis, University of Colorado Anschutz Medical Campus, and Director Lipid Clinic, University Hospital, Aurora, CO, USA (Dr. Eckel); and Bonow Professor of Medicine, Feinberg School of Medicine, Northwestern University, and Suzanne and Milton Davidson Distinguished Physician and Medical Director, Vascular Center of the Bluhm Cardiovascular Institute of Northwestern Memorial Hospital, Chicago, IL, USA (Dr. Stone)

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* Corresponding author.
E-mail address: editorjcl@lipid.org
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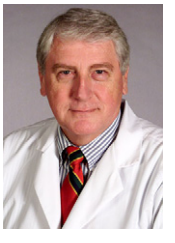
Opening/Introductions

The Roundtable discussion in this issue is between the Editor and three experts in the diagnosis and management of severe hypertriglyceridemic conditions. In most patients, elevated triglycerides are a marker of increased cardiovascular disease risk related to multiple changes in lipoprotein metabolism that affect low-density lipoprotein (LDL) and high-density lipoprotein (HDL) as well as the triglyceride-rich very-low-density lipoprotein (VLDL) and chylomicrons. However, there are patients whose triglycerides are so high that signs and symptoms develop and indeed life-threatening disorders follow directly from the latter lipoproteins. Drs. John Brunzell, Robert Eckel, and Neil Stone are Professors of Medicine and expert lipidologists in institutions that have a volume of patients allowing a large experience over many years with severe hypertriglyceridemia. I am privileged to have them together to discuss this problem.


Dr. Brown

W. Virgil Brown, MD: Let's begin by defining hypertriglyceridemia. Dr. Stone, what do you consider to be severe hypertriglyceridemia?

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Dr. Stone

Neil J. Stone, MD, MACP, FNLA: The ATP III guidelines, which are now more than a decade old, described normal triglyceride levels as less than 150 mg/dL, borderline-high triglyceride levels 150 to 199 mg/dL, high triglyceride levels 200 to 499 mg/dL, and very high triglyceride levels as 500 mg/dL or more.

Dr. Brown: I am thinking of plasma triglycerides that are causing or might cause symptoms and signs in the patient. Triglycerides greater than 500 mg/dL are called "very high" in our guidelines, but do such plasma concentrations lead directly to clinically significant symptoms and signs?

Dr. Stone: No. However, an important reason to consider a triglyceride greater than 500 mg/dL as very high is that above this level, causes of secondary hypertriglyceridemia (diet, drugs, diseases, or metabolic conditions) could dramatically increase triglycerides to a high enough level to cause pancreatitis. Drugs such as bile acid resins, estrogens, and steroids; marked alcohol and fat ingestion in a susceptible patient; or conditions such as poorly controlled diabetes or pregnancy can result in triglyceride levels greater than 500 mg/dL, which requires attention. It turns out that 500 mg/dL is a level that is quite uncommon in the National Health and Nutrition Examination Survey (NHANES) data that we looked at very carefully in the recent scientific statement on hypertriglyceridemia for the American Heart Association. There are a small but important number of people who have triglycerides in that range and they vary in ethnicity. For those in the NHANES survey with plasma triglycerides 500 mg/dL or more, approximately 1.4% were Mexican-American, 1.1% non-Hispanic white, and approximately 0.4% were non-Hispanic black.

Dr. Brunzell

John D. Brunzell, MD: In the NHANES study by Christian et al (see Suggested Reading), the authors estimated that 1.7% of adult U.S. population had triglyceride levels between 500 and 2000 mg/dL, or more than 3 million people, whereas only 80,000 people had triglyceride levels greater than 2000 mg/dL. My concept for definition of triglyceride levels is based on plasma concentrations above which the hypertriglyceridemia causes pancreatitis, that is, greater than 2000 mg/dL. I believe we should consider severe hypertriglyceridemia when values are greater than 1000 mg/dL because this places individuals at significant increased risk of pancreatitis. By not considering those at 500 to 1000 as at risk, we eliminate the vast majority of those between 500 and 2000 mg/dL. With values less than 1000 mg/dL, one should focus on the risk for premature coronary artery disease.

Dr. Eckel

Robert H. Eckel, MD: What's the highest triglyceride level any of us have seen? The highest level I've encountered is 29,000.

Dr. Brunzell: About the same for me.

Dr. Brown: My personal record occurred in a patient with a concentration of 26,500 mg/dL. I have been told of a patient presenting with 40,000 mg/dL.

Dr. Stone: Mine was also in the 25 to 29,000 mg/dL range.

Dr. Brunzell: What is puzzling is that some people with triglyceride levels of approximately 20,000 mg/dL do not develop pancreatitis.

Dr. Brown: The level that triggers an abdominal crisis varies greatly. Some can have pancreatitis at much lower levels than others; some can tolerate concentrations 10 times greater without pancreatitis.

It is with this in mind that I want to discuss the problem of triglyceride levels that should motivate the physician to do something about them quickly, in the next few days at most.

Dr. Brunzell: As an extension to a study by H. Schrott and me, republished in this issue of the *Journal*, we measured triglyceride levels in patients admitted for potential pancreatitis at the peak of their abdominal pain. There were two groups, one group with levels greater than 2000 mg/dL and the other with triglyceride levels below 900 mg/dL, with no one with values in between. The high group had multiple reasons for hypertriglyceridemia, and the second did not (see Brunzell and Deeb in Suggested Reading).

Dr. Brown: How about that, Dr. Eckel; do you agree that 1000 is the cut point that would be of concern in the clinic?

Dr. Eckel: I turned back to a chapter in the book *The Metabolic and Molecular Bases of Inherited Disease* (see Scriver et al in Suggested Reading), and there John showed that when TG levels are between 500 and 1000, some people are chylomicronemic and some are not, but at levels greater than 1000, everybody is chylomicronemic. Therefore, I like the term severe hypertriglyceridemia to be used when referring to levels greater than 1000. If the data are that levels greater than 2000 are when pancreatitis occurs, that's the first time I've been informed of this level. I have actually, of interest, reviewed a few papers in the last few months on severe hypertriglyceridemia and I am being swayed that it is greater than 1000; perhaps 2000 may be a better number?

But I think in terms of instituting a therapeutic approach, when people are at levels greater than 500, something needs to be done to prevent them from getting into more severely hypertriglyceridemic states.

Dr. Brown: I would agree with that summary, it is usually more than 2000 mg/dL before triglycerides perse' are the etiology of the signs and symptoms in a patient. If

they're less than 1000, I immediately assume that there's some other cause of the pancreatitis and not the triglyceride level.

Dr. Eckel: I agree.

Dr. Stone: I generally agree with that. I like the idea that before the patient gets to 1000, the physician has an important opportunity at 500 to 1000 mg/dL to intervene and especially regarding the patient's lifestyle, which can make an enormous difference. However, rigid cutoffs can be misleading. I have seen over the years at least three patients with known severe hypertriglyceridemia who presented with abdominal pain in the emergency room. In each case, I was told that the triglyceride was either 600 or 700 mg/dL but that the cholesterol was also very high, in the 500-600 mg/dL range. Because the suspicion in this setting was high for a much greater level of triglyceride potentially causing hyperlipidemic pancreatitis, I had the laboratory dilute the plasma. In these few cases, usually it was the middle of the night, it turned out the lab was wrong by a factor of about ten. The triglycerides were actually about 6000 and the clue was the 10 to 1 ratio between triglyceride and cholesterol.

Dr. Brown: Educating the physician to simply look at the blood sample is important. The plasma should look like cream.

Dr. Stone: Exactly.

Dr. Brown: If it looks like cream, it's not 600.

Dr. Stone: My caveat is that the number alone may not be enough. In fact, I think the laboratory technicians really have a responsibility in patients who present with abdominal pain and have elevated triglycerides to look at the tubes of blood. If it looks creamy, they've got to let the doctors in the emergency department know.

Dr. Eckel: I agree.

Dr. Brown: Okay. So, we have provided our definition of high concern, a concentration of triglycerides which should trigger some definitive action. So, now let's turn it around and consider the patient for whom we do not have a triglyceride measure. What complex of signs and symptoms. Would make you think about hypertriglyceridemia and what could you do immediately to assess that problem?

Dr. Eckel: Well, in the emergency department, presumably the patient has presented with abdominal pain, so if they have other symptoms, obviously you're not suspecting severe hypertriglyceridemia because that's the outcome about which we're most concerned. And again, I learned about a lot of this in Seattle—from Dr. Brunzell and others, but in a case of severe hypertriglyceridemia, in most people, an underlying genetic condition exists that ultimately is compounded by other metabolic factors that modify the severity of the hypertriglyceridemia. So, we think of the centrally obese metabolic syndrome kind of patient who may also have overproduction of VLDL and ultimately defects in lipoprotein lipase. In addition, there may be oral estrogens or other medications, an overly sedentary lifestyle, poorly controlled diabetes, alcohol, hypothyroidism, or other acquired factors that become superimposed on an already-existing genetic phenotype of moderate hypertriglyceridemia.

There's a whole cookbook of things that modify triglycerides. I think the clinician should remember that a triglyceride of 400 or 500 mg/dL can be elevated substantially and dramatically by many additional factors that modify triglyceride metabolism.

Dr. Brown: We have reviewed some of the historical elements that should suggest the diagnosis. What about recurrent unexplained pain in the past?

Dr. Brunzell: Certainly a patient in the emergency department with acute pancreatitis should be questioned about recurrent events and if they have a history of very severe hypertriglyceridemia.

Dr. Brown: We should also mention that a history of diabetes markedly increases the probability of severe hypertriglyceridemia. Recent weight gain can also be a factor.

Dr. Brunzell: In our patients presenting with recurrent acute pancreatitis and very severe hypertriglyceridemia, at least half have diabetes. They often first present with untreated diabetes; however, some will return with recurrent pancreatitis and treated diabetes after being placed on beta-blockers and thiazides for hypertension. Some also return after successful diabetes therapy and weight loss and develop acute pancreatitis with the subsequent weight regain. Other than diabetes, many drugs which interfere with the metabolism of triglycerides need to be considered in these patients.

Dr. Brown: It has been my experience that women who have hypertriglyceridemia that is asymptomatic for years can develop dangerously high triglyceride concentrations with a common dose of postmenopausal estrogen preparations.

Dr. Eckel: I think both Dr. Stone and Dr. Brunzell will agree that diabetes is perhaps the most common accelerator of triglyceride overproduction. With estrogen, it is the oral route of administration about which we're concerned. Cutaneous or vaginal administration does not have the same impact as oral estrogen, which increases hepatic synthesis of triglycerides perhaps because there is direct delivery through intestinal absorption and portal vein transport to the liver.

Dr. Stone: And then one other clue is a history of alcohol abuse. Alcoholic patients can get pancreatitis. That's one of the real common causes of pancreatitis, but alcoholic patients can present with severe hypertriglyceridemia and pancreatitis, and to not think of that is to potentially miss the complete diagnosis and the appropriate treatment.

Dr. Brown: That's really important. Patients seem to rarely associate their alcohol abuse with this problem.

Dr. Eckel: And, of course, alcohol is on that long list of acquired factors that can increase triglyceride production in the liver, right?

Dr. Stone: In addition to oral estrogens and alcohol, I would add recent attainment of their heaviest weight, recent indiscretion regarding the ingestion of high-fat foods, and/

or a recent addition of other medications that may increase triglyceride levels. The latter include bile acid sequestrants (really shouldn't start one if TG > 250 mg/dL), oral steroids, or isotretinoin for acne. In the susceptible person, these can all trigger a marked triglyceride response. As Dr. Eckel said, there's an entire list of medication relationships that are potentially important and should be investigated when pancreatitis with severe hypertriglyceridemia suddenly appears.

Dr. Brown: The medical history is always important and in this disorder usually contains these significant clues to etiology. Let us now turn to physical signs?

Dr. Stone, I recently saw a woman in the clinic with a rash. These turned out to be eruptive xanthomas on her back. She had been ignoring them. You often find these on the patient's back, upper neck, shoulders, upper arms and legs, and buttocks. If you do not roll them over when you find the patient lying on a bed in the emergency department complaining of the abdominal pain, this important sign can be totally missed.

Dr. Eckel: Yes, I had a patient in the clinic yesterday, Dr. Stone, with triglycerides of 1800 mg/dL. When she took her blouse off there were, eruptive xanthomas on her back. She had been ignoring them.

Dr. Stone: And Dr. Brunzell, I believe that these lesions, cutaneous xanthomas, have been shown to be clusters of foamy appearing macrophages in the dermis that contain fat droplets with composition like that in chylomicrons.

Dr. Brunzell: Yes, that was paper published by Parker et al. in *the Journal of Clinical Investigation* in 1970.

Dr. Brown: I believe he demonstrated that the fatty acids in the macrophages were characteristic of those consumed in a fatty meal. Is that correct?

Dr. Eckel: The thing I remember about this—is that there were a lot of cholesterol esters in those macrophages too.

Dr. Brunzell: When they biopsied them on presentation, the xanthomas were triglyceride-rich; when they biopsied them 2 weeks later, they had become cholestryl ester enriched−like foam cells.

Dr. Brown: They tend to come up in a matter of days, with a red base and a yellow center. After the triglycerides go down in the plasma, the yellow base disappears rapidly and the red, often pruritic base may take 2 weeks or more to resolve, leaving some dark pigment (melanin) in the area of the initial lesion.

Dr. Stone: That is consistent with my experience as well.

Dr. Brown: There's one other symptom complex that I've seen several times, and that is neurological symptoms. The patent may have paresthesias and even signs of peripheral neuropathy. Sometimes it's confined to the upper extremities, sometimes lower, and I have seen one case of organic brain syndrome with triglycerides greater than 20,000 that cleared up immediately as the triglycerides were reduced. That has also been described in the literature. So, both the peripheral nerves and the central nervous system can become involved. And my assumption has been that this is because chylomicrons actually plug capillaries in nervous tissue affecting most often the distal distributions.

Dr. Brunzell: Or maybe it occurs in tissues that contain lipoprotein lipase as Dr. Eckel has shown. We performed nerve conduction and memory studies in nine patients with very severe hypertriglyceridemia. These were patients with sensation in their hands, often described as "woody" and impaired recent memory. With lowering of their triglyceride, the paresthias and memory improved in all.

Dr. Brown: Exactly, and a layer of white creamy plasma floating on the top of the tube or even in the syringe as you draw the blood, should always accompany really severe hypertriglyceridemia.

Finding a big spleen goes along with the liver as well in some of these patients, so it can be hepato-splenomegaly. Macrophages as well as hepatocytes fill with fat in this condition.

I believe we have covered most of the symptoms and physical signs that should point to severe hypertriglyceridemia. I would now like to ask you about the evaluation of the abdominal pain.

Dr. Brunzell: It is likely that not all patients with lipemic plasma and abdominal pain have pancreatitis. Hepatosplenomegaly has been suggested to be the cause of pain in some patients.

Dr. Eckel: Well, I admitted a patient this week with lower abdominal pain that clearly wasn't pancreatitis. The TG was 14,000 on admission, but the pain was not pancreatic pain.

Dr. Brown: As I mentioned earlier, I am convinced that some of the presentations with abdominal pain are of intestinal origin because of classical symptoms and physical signs of borborygmus, migratory pain, and tenderness with quick resolution as the triglycerides decrease. However, in the emergency department and hospital, it seems evident that our major immediate worry is pancreatitis. What needs to be done to establish or rule out this diagnosis?

Dr. Eckel: This is clearly the most important issue when abdominal pain is the chief complaint. The evidence indicates that there's about a 1.5% to 3% rate of mortality from acute pancreatitis, and some of those patients may be severely hypertriglyceridemic; with hemorrhagic pancreatitis, people can die at home of shock; they may never get to the emergency department. So, when we see patients with pancreatitis and severe hypertriglyceridemia in the hospital, usually they have a good outcome because they're diagnosed and adequately managed. I think this is an area that the endocrinologist or even the astute primary care physician should know.

Dr. Stone: The absence of a large increase in plasma amylase can be very misleading. Lipases go up higher and seem to last longer, so if you're going to measure anything, finding elevated pancreatic lipase activity is the more

important enzyme to assess in the blood—but I think it's important to remember that studies of both show that they don't have high sensitivity, especially in the patient with abdominal pain who is a candidate for hyperlipidemic pancreatitis. Like so many important diagnoses in medicine, you need to avoid letting a negative test (in this case a normal serum amylase) deter you from reaching the correct diagnosis if other features suggest that hyperlipidemic pancreatitis is most likely.

Dr. Eckel: An amylase used to be a problem to measure in severely hypertriglyceridemic patients; thus, a lipase is the test of choice. I am not sure that's any longer true, but I never order amylase in a severely hypertriglyceridemic patient.

Dr. Brunzell: Today most clinical laboratories will clarify lipemic plasma by a short ultracentrifuge spin. In clarified plasma amylase and lipase usually are normal even though evidence by scan demonstrates pancreatitis. However, even these patients can develop very severe pancreatitis and elevated enzyme levels. Many years ago, I was involved with several patients with abdominal pain suggesting pancreatitis with normal amylase and lipase levels. At laparotomy, they were found to have hemorrhagic pancreatitis. Maybe there is something different about this kind of pancreatitis, such as small vessel disease versus ductal pancreatic disease.

Dr. Brown: In the past we have had difficulty with other chemical analyses in the laboratory. Triglycerides of many thousands would cause a problem in the past by displacing the plasma compartment and artifactually lowering the measured water soluble component of the blood such as sodium, potassium, and enzymes. I understand that the newer laboratory equipment corrects for this and these measures now reflect the concentration in the water space of the plasma, Are there other tests that may be misconstrued based on the high triglycerides?

Dr. Stone: I think it depends on the equipment. You really have to be very careful. In the severely hypertriglyceridemic patient, you should be suspicious of artifact and you may wish to have the lab either dilute the serum or check it later after the triglycerides are lower because you could get severely misled by certain tests.

Dr. Brunzell: I would agree. Many of the past difficulties are now history. Most laboratories will spin the sample to remove chylomicrons and then run sample, this is termed "clarification of plasma".

Dr. Stone: But you first have to be aware that that's the issue.

Dr. Brunzell: Hopefully when today's laboratory technicians see the milky plasma and they clarify the plasma.

Dr. Brown: What if pancreatitis is consistent with your physical findings and history? What is the best way to make the diagnosis?

Dr. Brunzell: In very severe hypertriglyceridemia, when you have a patient who you think has triglyceride-induced pancreatitis for the first time, you diagnose them by imaging.

Dr. Brown: That's extremely important. If you suspect pancreatitis, that's the definitive test in the modern world.

Dr. Brunzell: When significant pancreatitis is present, you can see intrapancreatic and peripancreatic edema, either with magnetic resonance imaging or computed tomography, even though the amylase and the lipases are normal.

Dr. Brown: I agree, if there is upper abdominal tenderness and the pancreas appears swollen and edematous on an appropriate imaging study, you must assume you have pancreatitis and treat accordingly. The absence of a confirmatory clinical laboratory test should not dissuade you from that course. What about the genetics of this disorder? Is this always a genetic disease with superimposed environmental influences?

Dr. Brunzell: We studied 52 patients with pancreatitis and very severe hypertriglyceridemia (triglycerides $>$2000 mg/dL) and their families (see Chait et al in the Suggested Reading). All 52 had hypertriglyceridemic relatives, but the hypertriglyceridemia was much milder in their family members. Approximately 90% of the probands had an identifiable secondary cause for hypertriglyceridemia as well. Recently, Hegele has suggested that there are a small number of gene variants that are more common in these people. It is possible that patients with these minor background genetic variants may be more susceptible to getting very severe hypertriglyceridemia along with other genetic and environmental causes (see Johansen and Hegele, Suggested Reading). In treating such patients you've got to do at least two things: you've got to assume there's a genetic lipid disorder (which may be responsive to treatment with a fibrate), and you need to look for the secondary lipid disorder that you also can treat.

Dr. Stone: Dr. Elliott Joslin, many years ago, stated that "genetics loads the gun but environment pulls the trigger." I think that's a really good thing to remember when you see these people. Dr. Brunzell's admonition that these problems occur when an acquired or secondary triglyceride elevation occurs in a susceptible patient because of their genetic makeup can't be stressed enough.

Dr. Eckel: Well, I just wanted to kind of remind us all of basic enzyme kinetics. If the genetic determinants of substrate production and enzyme activity are compromised and the triglyceride clearance is already near capacity due to these abnormalities in enzyme kinetics, a modest environmental or pharmacological insult may take the system above saturation kinetics. This means that the triglyceride concentration can rise from a few hundred to several thousand mg/dL over a short period. These extra influences that we have discussed, when present in people with genetic susceptibility and who are already moderately hypertriglyceridemic may get into trouble with severe hypertriglyceridemia. On Friday the triglycerides may have been 550 and then the Super Bowl and a case of beer intervened while the patient sat on the couch all weekend could result in TGs of 2200 mg/dL on Monday morning. It doesn't take you very long to get into trouble when the system is already near saturation kinetics.

Dr. Brown: Are there iatrogenic triggers for patients already in therapy for this condition?

Dr. Brunzell: One of the things that's critical to tell the patients is never stop their fibrates intake abruptly because it only takes about 24 hours for the triglyceride can go up several fold.

Dr. Brown: The impact of discontinuing fibrates can be several weeks in duration and that's a good point. What about losing control of diabetes, such as stopping insulin or other hypoglycemic medications?

Dr. Brunzell: Once the diabetes is being treated, the hypertriglyceridemia is easier to control because it's mostly now attributable to hepatic overproduction in a saturable system. Many people who are severely hypertriglyceridemic when they're entirely untreated also have a defect in adipose tissue lipoprotein lipase. Where I think the problem comes with recurrent acute pancreatitis in the diabetic is treatment for hypertension with beta-blockers and thiazides, particularly in the past. And the other thing is if the physician says I want you to lose weight and they lose weight and they gain it back and they get pancreatitis while they're regaining the weight.

Dr. Stone: I would add that beta-blockers are important drugs for patients with indications in acute and chronic ischemic heart disease, heart failure, and arrhythmias and elevated blood pressure in those with heart disease. Carvedilol may be a useful choice over metoprolol in those patients with elevated triglycerides because of its different metabolic profile. Thus, the choice of a beta blocker can matter.

Dr. Brunzell: In a patient who's got normal triglyceride or mildly elevated triglyceride levels, beta blockers don't have a very great effect, but if the triglyceride concentration is around 500 or 800 and then a beta blocker or thiazide is introduced, you double your triglycerides; if you go on a beta blocker *and* a thiazide, you quadruple it (see Brunzell and Deeb, Suggested Reading).

Dr. Stone: Exactly. But if a beta blocker is needed, carvedilol is a better choice for these patients in my experience. Although for patients with hypertension and without known cardiovascular disease, substituting for the beta blocker may be especially useful in the patient with high triglycerides.

Dr. Brunzell: We should teach physicians to be careful when they use oral estrogens, vitamin A derivatives, beta blockers, thiazides, as well as antiretroviral protease inhibitors in patients with triglyceride levels between 1000 and 2000 mg/dL. When we manage cardiovascular risk factors and other disorders in hypertriglyceridemic patients, we must be on guard when we consider these drugs. Protease inhibitors are a special case because they are not easily and fully substituted by other effective agents when treating HIV. You cannot get around that. But when one is prescribing antihypertensive agents and medications for ovarian failure in patients with high triglycerides, the avoidance of certain classes of medications may be critical.

Dr. Eckel: I agree. If your triglycerides are 90 and you're put on a thiazide diuretic or another drug, it may increase triglycerides to 105 to 110 mg/dL. The concept is that such drugs, in their own right, don't cause much increase in plasma triglycerides, but when they're superimposed in someone who already has moderately severe hypertriglyceridemia, then we can get into trouble.

Dr. Stone: I would like to emphasize the difference between a marker and a target. Triglycerides are a useful marker for a variety of metabolic conditions that include metabolic syndrome or a familial genetic disorder. Therefore, before you turn a mild elevation in triglyceride levels into a target, try to consider what they are actually signifying.

Dr. Brown: An uncommon problem but one that is quite difficult to manage comes with the major gene defects that can present with severe hypertriglyceridemia. Dr. Eckel, would you give us your view of this issue?

Dr. Eckel: Well, most of these patients have lipoprotein lipase deficiency and there are a few mutations in exons 5 and 6 that characterize the genotype in these patients. True homozygotes are rare; most of these patients are compound heterozygotes. They just don't have the same allelic defect from their mother and father. Some of the mutations are in the catalytic triad, which is the location where the lipase carries out hydrolysis of the triglycerides in chylomicrons and VLDL triglyceride, but some are in the heparin-binding domain of the molecule. Then there's apoC2 deficiency, which some people have found to be less severe and seemingly less common. This disorder may be more difficult to define since few laboratories can measure apoC2, but if post-heparin plasma has lipoprotein lipase (LPL) activity and the patient is a young child with severe hypertriglyceridemia, you should look for other causes, and apoC2 could be one. Bovine lipoprotein lipase in fresh milk can be activated by the patient's plasma if apoCII is present and this can be used as a test for this activating apolipoprotein.

A final genetic defect is the protein identified by Steve Young's group—this glycophosphatidylinositol (GPI)-anchored HDL-binding protein that helps anchor LPL to the endothelium is essential for LPL activity in vivo. Since the identification of this protein, a few cases of GPI HDL-binding protein deficiency associated with severe hypertriglyceridemia have been identified.

Dr. Brunzell: Other essential components of the system include apolipoprotein A5 and lipase-modulating factor-1 (LMF1). A rare patient has been described with defective function in these as well. But with regard to frequency of occurrence, I would agree that LPL is the most common major gene defect that leads to severe hypertriglyceridemia. To put numbers on it, I've been involved in the care of approximately 300 patients with LPL deficiency, with no activity and a genetic defect. I've seen two apoCII-deficient patients and no apolipoprotein A5-deficient, GPIHDLBP1, or LMF1 patients. To put it into perspective, LPL deficiency, as Dr. Eckel said, is the name of the game in

kids, after you rule out these indeterminate mild hypertriglyceridemic states with superimposed metabolic disorders and/or iatrogenic insults.

Dr. Brown: Now that we have reviewed several etiologies of severe hypertriglyceridemia, I would like to return to the question of the pathophysiology of pancreatitis related to chylomicronemia.

Dr. Eckel: Why do triglyceride-rich lipoprotein particles cause pancreatitis? That question is one I don't think any of us can definitively answer from the experimental data we have. There's an old concept that I think is still reasonably valid that these large particles get trapped in pancreatic microvessels, which results in infarction and intracellular release of pancreatic lipase that further damages the pancreas by auto digestion.

Dr. Brown: I believe that is a viable theory.

Dr. Eckel: But the thing about that is why the pancreas only? You don't have the same pathophysiology in the lung, kidney, or for other organs, but of course there's no pancreatic lipase there.

Dr. Brown: Well, mice that have lipase deficiency as the result of genetic LMF1 deficiency die because they plug up their pulmonary capillaries. They don't develop pancreatitis, but they became increasingly cyanotic as the result of reduced oxygenated hemoglobin.

There are several theories as to why hyperchylomicronemia can cause pancreatitis or dysfunction in other tissues. There are old data from studies in the rabbit demonstrating that high concentrations of chylomicrons generated by a large fatty meal can actually plug capillaries transiently. If this occurs in the human, as noted by Dr. Eckel, it could literally cause ischemia at the microvascular level leading to leakage of pancreatic enzymes into the body of the gland. Similar reduction of blood flow might cause the intestinal and nervous system disorders that we have previously discussed. Of course, chylomicrons have a coating of negatively charged proteins such as apolipoprotein CIII, which probably help prevent aggregation. I have previously speculated that these phenomena might occur when the number of triglyceride rich particles (and their surface area) is too great for the available apolipoproteins to provide the repulsive forces that keep chylomicrons apart.

Dr. Brunzell: Part of the problem is red cells get through very easily and think of the relative size of a red cell compared with a chylomicron.

Dr. Brown: I agree, that means a large clump, consisting of many chylomicrons would be required.

Dr. Brunzell: You mean it's clumped in vivo?

Dr. Brown: Yes. The living rabbit can be equipped with an ear chamber consisting of slides clamped to an area of denuded skin. With a microscope, you can watch the blood flow through the capillaries. Chylomicrons have been shown to plug these small vessels after placing fat in the stomach of the animal.

Dr. Eckel: Oh, chylomicrons can get up to 7 or 8000 angstroms in size.

Dr. Brown: Then let me summarize my earlier conjecture. That pancreatitis might be caused by microvascular ischemia as the result of chylomicron clusters plugging capillaries followed by cell necrosis and release of pancreatic enzymes into the extracellular spaces of the gland. Pancreatic lipase with release of high concentrations of fatty acids from the chylomicrons in regions of stasis could be contributory as suggested by Dr. Eckel. All of this is hypothesis that needs some imaginative research.

Dr. Brunzell: Be that as it may, the patient does better with a low-calorie, fat-free diet, no matter the etiology of the chylomicronemia including those patients with LPL deficiency.

Dr. Eckel: The other thing I think we shouldn't forget is that people with repeated bouts of pancreatitis may have pancreatic pain chronically, and in some it's the pseudocysts that can follow pancreatitis which can also cause pain. These people may not have acute pancreatitis but have abdominal pain that has historically been related to pancreatitis.

Dr. Brown: That's right. Once you've had a bout of really severe pancreatitis, you're subject to recurrent pancreatitis without severe hypertriglyceridemia, and these later bouts may not have an obvious trigger. It seems to spontaneously occur, probably because of so much damage—scarring and partial tubular blockage of the ductal system of the pancreas.

Dr. Eckel: This is perhaps a bit mythical, but once you've gotten your first bout of pancreatitis, you're more susceptible to recurrent pancreatitis. That has been my experience.

Dr. Eckel: In the emergency department, you see your chronic alcoholic patients with a history of alcohol-induced pancreatitis in with acute pancreatitis and they claim they've only had a couple of beers the night before. Well, it may not take quite as much alcohol to have recurrent pancreatitis in this setting, but I don't know for certain.

Dr. Brown: Getting through the first episode of pancreatitis and controlling the triglycerides with values less than 1000 mg/dL may not prevent the syndrome of chronic recurrent pancreatitis. I have seen that over the years, even in those abstaining from alcohol.

Dr. Brown: Let's talk about the later phases of management. We have the patient in the hospital. We have determined that he's got pancreatitis. We treat the pancreatitis in the usual way—with intravenous fluids, nothing by mouth (NPO) for a few hours, and no fat for a few days. What are the important points in making this transition?

Dr. Eckel: There's no question with acute pancreatitis, the patient should be NPO until pain is controlled. Then they're either NPO or ultimately on a no-fat diet or a liquid diet that's fat-free for a few days. The natural history of inpatient pancreatitis from severe hypertriglyceridemia is a 4- to 5-day admission typically.

The other question is how fast will the triglycerides fall in that setting, and Dr. Brunzell's got much more experience

with LPL deficiency in such a setting than I do. However, in adults with severe hypertriglyceridemia, the predicted decrease per day with this regimen, and without intravenous insulin or heparin, is about 20% to 25% per day.

Dr. Brunzell: Yes. There is a difference between LPL-deficient patients whose levels decrease rapidly and adults with very severe hypertriglyceridemia who don't have LPL deficiency.

Dr. Eckel: Dr. Brunzell, do you think that potentially this could be due to the insulin resistance in this metabolic environment? In other words, perhaps the VLDL TG production rate is greater and lipolysis rates are greater?

Dr. Brunzell: I do not know of any data to answer that question. The appropriate action to speed the decrease in triglycerides depends on what's going on with the patient. If they're on a beta blocker, you stop the beta blocker. If they are on accutane and you stop, if they're on estrogen, you stop. The pain is present for a while. So, it really depends on the patient. I am not sure that I know what insulin resistance does in the syndrome.

Dr. Eckel: Do you think that intravenous insulin is beneficial in the absence of diabetes?

Dr. Brunzell: No, not in the absence of diabetes.

Dr. Eckel: Do you think it's valuable in the patient with diabetes or poorly controlled diabetes? I drip these patients myself.

Dr. Stone: Dr. Eckel, in the patient who's diabetic, an insulin drip makes sense and in my experience over a few decades, one can make a big difference in the speed of recovery.

Dr. Brown: I would agree. And careful management of the plasma volume and electrolytes with potassium and sodium control as well as management of occasional hypocalcemia is important also. After we have controlled their pain, the blood glucose, electrolytes and the triglycerides, we must plan the transition to outpatient status.

Dr. Brunzell: We must find and correct the secondary causes before discharge.

Dr. Brown: Correct, we have taken away every treatable cause we can identify. The patient is doing well and we have measured their triglycerides. Is here a level that would allow them to have a more normal diet, expecting to see a continued decline of the triglyceride concentration in the plasma?

Dr. Eckel: First, let me share with you something that's anecdotal, and it's something I've done frequently in the last 10 years plus, and that is not giving triglyceride-lowering drugs until triglycerides are close to 1000 mg/dL. The reason for this is two-fold; first, I want to indicate the importance of a dietary modification to get rid of the chylomicronemia, and, second, when the patient's triglycerides are ~1000 to 1200 and I give them a fibrate and/or omega-3 fatty acids at high dose, triglycerides decrease very quickly. In this scenario the patient sees that the drugs they may have been taking do work. Most often many of these patients have been on a drug before they present, but believe the drugs have failed. That's because they've gotten into saturation kinetics, and now, dietary fat is like a faucet still turned on with a small drain hole. When the sink is full, we need to reduce the inflow to better match that of the drain and let the water level fall. With triglyceride-lowering drugs we then reduce the level further and the triglyceride inflow can be adjusted to the lipolytic clearance process.

So, the idea here is that the drugs don't work much on LPL but reduce VLDL production rates by the liver. When chylomicrononemia is present, LPL is saturated and the effect on the liver is not apparent.

Dr. Brown: So, the drugs don't work on the gut. What you've got to do is take the fat out of the gut first—prevent the generation of chylomicrons and then the drugs work in the liver to reduce the endogenous production rate of triglycerides. I must also point out that fibrates not only reduce triglyceride synthesis in the liver but also reduce the synthesis of apoC3. This protein has an inhibitory effect of clearance in both animal models and in humans. Turnover data in humans also demonstrate that fibrates enhance clearance of triglyceride rich lipoproteins.

Dr. Eckel: Right.

Dr. Stone: I agree with what Dr Eckel just said, but if the situation seems clear cut—you have a patient with a hypertriglyceridemic father and he's on accutane you stop the accutane, and often if there is good adherence to lifestyle recommendations, you may not need to add medications to lower triglycerides. Some patients have ongoing factors such as diabetes, sedentary behavior, and poor diet all together and then triglyceride-lowering medication may be very helpful in preventing the patient from presenting with recurrent severe elevations in triglycerides while you work on improving adherence to lifestyle change.

Dr. Eckel: After an abdominal crisis and hospitalization, how frequently should these patients be seen and when do you modify the diet? Here's my rule of thumb. It's now 3 days after discharge from the hospital, presumably after instituting the fibrate and/or the high dose omega-3s before or on discharge. At this 3-day time point, I get triglyceride measurements because, as Dr. Brunzell pointed out, triglycerides change quickly. This is not LDL, with a half-life of 3.5 to 4 days. Once I can prove that the triglycerides are at a comfortable level—let's say around 500 mg/dL, then we have a challenge nutritionally. So, Dr. Brown, how do people then respond to carbohydrate restriction vs. continued fat restriction? I tend to gradually introduce more fat into the diet going forward, but if the triglycerides go up, then I am going to have to deal with the carbohydrate. Unfortunately this is outpatient medicine, and in the outpatient setting you can tell the patient what he or she should do, but whether they're doing it, we have no proof.

Dr. Brunzell: I would focus on simple sugars, rather than all carbohydrates.

Dr. Brown: At this point, I believe the key element is calorie restriction in the patient with no major genetic defects such as LPL deficiency. We must not only reduce triglyceride delivery from the gut but also synthesis in the liver. Reduced calories are the means of doing the latter. I

tend to emphasize saturated fat restriction and slowly liberalize the unsaturated fats as the triglycerides decreases to less than 500 mg/dL. It is true that very high-carbohydrate/fat-restricted diets tend to increase hepatic production and therefore, a diet containing 20% to 25% fat is best on discharge. If weight loss is achieved and the triglycerides decrease further, the fat can be liberalized but weight gain is a warning sign that the patient is headed for trouble that the drugs may not control.

Let me return to the acute management in the hospital. Is there any place for heparin infusion in such patients?

Dr. Eckel: I gave my recent patient with a triglyceride concentration of 14,000, 100 to 200 units of heparin during the intravenous insulin infusion. Whether that does anything, I don't know. I have no idea.

Dr. Brunzell: Let me address that. There is no physiologic reason to think it's going to work. If you infuse 100 units, 200 units of IV heparin, draw an EDTA tube, which you which you set aside, when you measure triglyceride there is a tremendous decrease in triglyceride. If you collect the sample in orlistat, which is a lipase inhibitor, triglyceride doesn't change. The apparent decrease in triglycerides occurs after the blood is drawn.

Dr. Brown: I have been concerned that if you do have hemorrhagic pancreatitis, you may cause intra-abdominal bleeding that makes the vascular crisis worse. So, I've never used heparin for those reasons.

Dr. Stone: And even those who promote it, if you look at their timeframe, it's such a short-lived intervention. It seems to me the benefit risk ratio isn't there, and I agree with Dr. Brunzell that it's just hard to support heparin infusion with current data.

Dr. Brunzell: I've given up to 60 units per kg per hour for 8 hours in a research protocol. It doesn't lower TG dramatically.

Dr. Eckel: Well, presumably with that dose, you've released all of the lipases including hepatic lipase, LPL and endothelial lipase.

Dr. Brunzell: We measure lipase activity on an hourly basis and it is maintained for the full duration of the infusion. The dose of 60 kg per kg per hour is required to maintain lipase levels.

Dr. Eckel: Presumably, the cells make LPL and continue to release it into the plasma at a rate equal to the clearance of the enzyme with that dose of heparin as a continuous infusion.

Dr. Brunzell: Yes. Now, I'd like to know what other people think about plasmapheresis to lower triglycerides in the hospital. I am very much opposed to this treatment.

Dr. Brown: Some have used lipopheresis by applying the HELP system or the Kaneka device. I've never done that. It never seemed necessary because, as you say, if you manage the patient properly, triglycerides fall very rapidly.

Dr. Stone: Well, we had a case of hyperlipidemic pancreatitis triggered by chemotherapy for graft versus host disease that didn't respond to intravenous insulin or lipid lowering medications. The triglycerides were about 17,000 so, we commenced with plasma exchange (we didn't use an apheresis system) with success in greatly lowering her triglycerides. I don't use plasma exchange often, but in refractory cases such as this, it was very helpful.

Dr. Brown: Did she have diabetes also?

Dr. Stone: Yes, she had steroid-induced diabetes.

Dr. Stone: I had another person who, likewise, and was very sick with hyperlipidemic pancreatitis and triglycerides in the 10,000 mg/dL range. He has since become diabetic and hypothyroid, but when he presented he had none of these present. Again, plasma exchange dramatically improved his clinical picture, so I am reluctant to say this can't be useful in selected cases. But I would point out that these are a few cases and not the routine.

Dr. Brown: Well, we have the Kaneka system at Emory. I have never attempted to use it in this setting, so I have no experience with this.

Dr. Brunzell: They claim it clogs the filter.

Dr. Brown: Really? So, it won't flow after a while.

Dr. Stone: I would definitely agree that plasma exchange for those with triglyceride levels so high in the setting of acute pancreatitis or felt to be greatly at its risk is not a routine procedure and would use it only in circumstances in which a person with lipid expertise thought it would be useful.

Dr. Brunzell: We should recommend this only under very unusual circumstances.

Dr. Brown: I think we have covered the acute syndrome. Now let's talk about the longer-term management. Once you've documented that this patient has had severe hypertriglyceridemia and all the consequences, how do we keep the triglycerides at an appropriate level?

Dr. Brunzell: Well, the first thing is to educate them about why they got very severe hypertriglyceridemia in the first place. The second thing I do is I give them a list of all the drugs to avoid. That takes care of 90% of it. I don't keep them on a chronic low-fat diet anymore, except for the antiatherosclerotic needs.

Dr. Brown: Is there anything about the diabetes in this type of patient that's special? Would you choose certain drugs versus others to manage the diabetes because of the severe hypertriglyceridemia?

Dr. Eckel: I think if we look at the relationship between hemoglobin A1C and triglyceride metabolism, I have the sense that between an A1C of 5.7%, putting people at risk for diabetes, up to 7.0% there's not much change in TGs. TGs may be slightly greater at 6.9 than they are at 6.1, but there is little difference. Once you get to ~7.0%, that slope starts increasing and I believe that is mostly the result of increases in VLDL production. LPL decreases with more severe loss of diabetic control. From previous work, both muscle and adipose tissue LPL go down in the poorly controlled patients with diabetes. So, in terms of managing diabetes, I want the A1C around 7.0% or less, you give the best kind of diabetes management in terms of triglycerides. Now drugs, I think it may influence

your decision for diabetes-directed drug therapy. We know that one TZD, pioglitazone, may have modest TG lowering effects; however I wouldn't use it just for this purpose. Overall, insulin probably is best.

Dr. Brown: Both rosiglitazone and pioglitazone lower plasma fatty acid concentrations and yet only pioglitazone lowers the triglyceride concentration modestly in stable diabetics. Of course, those observations were made my Dr. Ronald Goldberg in diabetics without severe hypertriglyceridemia.

Dr. Eckel: And there are 11 classes of drugs to treat diabetes now, and a peroxisome proliferator-activated receptor-alpha agonist would not be one of them.

Importantly, DPP-4 inhibitors have no effect on triglycerides. Moreover, metformin has minimal, if any, effects on triglycerides. So, I think you're pretty safe going with any agent, but if the patient cannot be adequately controlled, as stated previously I would go to insulin. The GLP-1 agonists are, I think, a promising area and if people are losing weight, then their triglycerides will come down with the weight reduction. So, I think the weight loss may make me favor a GLP-1 receptor agonist.

Dr. Stone: I think you need to empower the patient with specific knowledge about elevated triglycerides because some patients have bounced from hospital to hospital and every doctor seems to have a different regimen. As stated by Dr. Brunzell, they need to know more about the effects of diet and which medications may trigger the disorder as well as those medications that can keep them out of the hospital. You need to build into this approach a program to encourage compliance with lifestyle behaviors that reduce coronary risk as the result of improvement of metabolic risk factors.

Dr. Eckel: I believe that people who have had severe hypertriglyceridemia need to be referred to a lipid specialist to obtain a better understanding of what caused this, what needs to be done, and why. And of course, it is very important to provide more information to the primary care physician how he or she may prevent this metabolic catastrophe.

Dr. Brunzell: I agree entirely. Patients who have had severe hypertriglyceridemia and are properly managed can go for years, probably for the rest of their lives, without another occurrence of signs or symptoms.

Dr. Brown: Weight loss can be extremely important in people who are overweight, wouldn't you agree? Again, weight loss reduces VLDL triglyceride production rates.

Dr. Brunzell: For diabetic patients I wouldn't agree. Weight loss is very effective in lowering TG levels. If we had a method to take weight off and keep it off, this would be effective. However, obese patients regain the lost weight, then redevelop very severe hypertriglyceridemia and recurrent acute pancreatitis.

Dr. Brown: I believe the regain is another issue. Even those who regain are often below their projected weight if there is no intervention.

Dr. Brunzell: The use of GLP-1−enhancing drugs may help overcome this tendency to regain the weight.

Dr. Eckel: I agree with that.

Dr. Brown: There are programs that seem to produce a significant weight loss and although it's true that most have regained over the first or second year, but if you compare to an untreated control group, they are still less obese at the end of many months of observation. I believe that can be helpful. I also like using GLP-1 drugs for this purpose in diabetics.

Dr. Brunzell: In the Diabetes Prevention Program in patients with impaired glucose metabolism, most of the weight, but not all, was regained in follow-up.

Dr. Brown: That's the point. Not quite to baseline, so if you make them a little thinner, and with some exercise—there is benefit. However, I also must agree that this is a very difficult matter with too little success.

Dr. Stone: I do see cases that do remarkably well. Often, it depends on whether the patient is enrolled in a "system" that works for them. I tell patients something I learned from a wise patient years ago. He remarked that a good system makes a good employee great and a great employee outstanding. Similarly, patients who adopt a good system for complying with lifestyle changes in my experience have a better chance to maintain lifestyle changes. Without this, I agree that the majority of patients fall off the wagon within a year.

Dr. Brunzell: I agree, and that's why the Diabetes Prevention Program (DPP) was so important. These diet and exercise people had the best of all systems for weight loss, and still most of the lost weight was regained over time.

Dr. Stone: But Dr. Brunzell, in the Finnish Diabetes Prevention trial, they still had good results when they published an 8-year follow up. In that intervention trial that used lifestyle approaches, an approximately 36% reduction in diabetes incidence remained after the individual lifestyle counseling was stopped.

Dr. Brunzell: The trouble is people dropped out and they weren't counted. I have no problem with somebody, for example, who's an athlete and then goes to work at a job at a desk, and I very much push them for aerobic exercise with a low-fat diet and I try to help them maintain that, but that's not the kind of patient we're talking about. We're talking about a 50- or 55-, 60-year-old person.

Dr. Brown: We should try to tailor any therapy to the patient. I believe one should attempt to use good judgment in prescribing therapy, considering that which the patient will or will not accept.

Are there any other points about long-term management that you would like to discuss?

Dr. Brunzell: I believe that to properly manage these patients, one should set a goal with the patient of maintaining levels of triglycerides less than 1000 mg/dL. If they go above that value, a change in the regimen should be considered. As Dr. Eckel pointed out, they have saturated their clearance system and a minor insult can take them into very dangerous levels.

Dr. Stone: That's the reason why I like the 500 mg/dL. You have a margin for error. I really don't want them living at a triglyceride of 1000. They are too close to the edge of catastrophe.

Dr. Brunzell: As mentioned earlier, Christian et al. using NHANES data estimated that more than 3 million

U.S. citizens have triglyceride levels between 500 and 2000, whereas only 80,000 are at levels greater 2000 mg/dL. Do we treat the 3 million to prevent the severe hypertriglyceridemia, or do we educate them about how not to develop such high TG levels? I would prefer a treatment level around 1000 or perhaps 1500 mg/dL.

Dr. Stone: I think it's possible that some people who were in the 500 to 1000 range can do remarkably with lifestyle change, getting rid of triggers. I recall one person who stopped her hormones became much more active, had modest weight loss, and her triglycerides decreased to quite low levels. These levels can be treated with some attention to detail.

Dr. Brunzell: Yes, I am not disagreeing with that. In fact, I am agreeing with you 100%. But what people are saying is that these people should have drugs specifically for lowering their triglyceride and that's what I am talking about.

Dr. Stone: Understood.

Dr. Brown: However, I believe drugs are often appropriate and there is an art to using the few drugs we have for this condition. In this setting I have seen patients who responded partially to fibrates but who responded remarkably to niacin. The opposite can also be observed. Patients who don't respond to niacin very well will respond to fibrates. Others are remarkably responsive to omega-3−containing fats. I don't know how to predict who those people are without trying the drugs in some logical order. So, I believe that you should be willing to change the triglyceride-lowering drugs based on observations with the patient. In most cases, I view large doses of omega-3 fatty acids as add on therapy when the first two drugs do not produce a satisfactory result. Let me ask each of you, should all these people be put on 4 grams of omega-3 fatty acids if they've had triglycerides in the 1000 or 2000 or higher range?

Dr. Eckel: Not all.

Dr. Brunzell: Patients with LPL deficiency are one particular subset who have further elevation of TG levels with fish oils, at which time they often develop pancreatitis again. I have no doubt that fish oil lowers triglycerides. It is only the people with major gene defects in the lipolytic system that may be harmed with fish oil. This is because the fish oil also provides substrate for chylomicron triglyceride. The chylomicrons have fish oil fatty acids in them.

Dr. Eckel: Is this enough fat to cause problems in these people? We are talking about only 4 grams of DHA and EPA.

Dr. Brunzell: Well if you add 6 grams of fat to a fat restricted diet, the total fat load may be increased by 50%.

Dr. Eckel: I am skeptical.

Dr. Brunzell: Well, let me say this; one quarter of the people who are referred to me and documented to be LPL deficient by our clinical assay for LPL are on fish oil.

Dr. Eckel: But the omega-3s reduce VLDL production.

Dr. Brunzell: Except the pancreatitis is caused by the chylomicrons, not the VLDL. VLDL secretion seems to be suppressed in LPL deficiency.

Dr. Brown: In most cases, the clinician is faced with severe hypertriglyceridemia in persons with lipoprotein lipase deficiency. It may be that changing the VLDL synthesis will reduce the saturation kinetics we discussed before and thereby allow some margin for increased intestinal delivery of chylomicrons into the plasma?

Dr. Eckel: It seems, Dr. Brown, Dr. Stone, and I are both comfortable under 500. Dr. Brunzell's OK up to 1000.

Dr. Brown: Sometime you have little choice but to continue to observe values over 500 mg/dL. There are people that I've followed for years whose triglyceride concentrations are continuously near 1000 mg/dL.

Dr. Eckel: So have I.

Dr. Brown: And they never get pancreatitis. They just stay there, and worry me. I haven't derived a regimen to cure that in these specific patients.

Dr. Eckel: But aren't you more comfortable at 400 than you are at 900?

Dr. Brown: Oh, absolutely, the lower the better. In these patients, would you use fish oils (omega-3 fats) if the patient maintains plasma concentrations of 500 to 1000 mg/dL on a medical regimen?

Dr. Eckel: Yes, Dr. Brown, and I think in many of these people with severe hypertriglyceridemia—and I agree with Dr. Brunzell wholeheartedly, you need to correct secondary causes as much as you possibly can. Once you've done that, if TGs are in that higher range, they need at least two drugs, fibrates and oils containing omega-3 fatty acids. I have some people on niacin and high-dose potent statins too, eg, rosuvastatin 20-40 mg daily.

Dr. Brown: That's been my experience too. Even when the LDL is quite low, in these people and triglycerides are greater than 500, and on a fibrate or niacin, a dose of statin at as low as 5 mg or 10 mg would further lower triglycerides quite significantly.

Dr. Brunzell: The LDL cholesterol may be 25 though.

Dr. Brown: That's right, but that is not harmful. The issue is preventing pancreatitis and the statins really help in further lowering triglycerides when added to fibrates or niacin.

Dr. Eckel: I agree.

Dr. Brown: Gentlemen, thank you for this discussion of your knowledge and experience in managing severe hypertriglyceridemia. This is a problem that is very hard to study and the cases differ so dramatically, the experience of personally diagnosing and treating these patients provides for very useful information for many physicians who have not had the opportunity that has been afforded to each of you. I want to again call attention to the article from Drs. Brunzell and Schrott that has been reprinted in this issue. This is one of the very few publications reporting on patients who were monitored systematically after presenting with abdominal crises related to severe hypertriglyceridemia.

Suggested Reading

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