

Type III Hyperlipidemia

Information for Patients

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What is Type III hyperlipidemia?

Type III hyperlipidemia is a rare kind of combined hyperlipidemia, in which both cholesterol and triglyceride are increased in the blood. Though rare, Type III hyperlipidemia is particularly important, since it leads to accelerated atherosclerosis, which causes heart attack, stroke, or blockage of leg arteries at a young age. Other names for Type III hyperlipidemia are Type III (or Type 3) hyperlipoproteinemia, dysbetalipoproteinemia, or remnant hyperlipidemia.

Type III is different from the common kind of combined hyperlipidemia in the following way: Ordinarily, almost all of the triglyceride in the blood is carried in large fatty particles, lipoproteins, which contain predominantly triglyceride and very little cholesterol. These triglyceride-rich lipoproteins are very low density lipoproteins (VLDL) and chylomicrons. In the same way, most of the cholesterol in the blood is carried in smaller fatty particles, called low density lipoproteins (LDL), which contain predominantly cholesterol and very little triglyceride. The common type of combined hyperlipidemia is a mixture of these ordinary lipoproteins. The common type of combined hyperlipidemia has high levels of both large triglyceride-rich and smaller cholesterol-rich lipoproteins. These are the usual lipoproteins found in the blood, but they are present at abnormally high levels in common combined hyperlipidemia.

In contrast, Type III hyperlipidemia has greatly increased levels of remnant lipoproteins. Each remnant lipoprotein contains almost as much cholesterol as triglyceride. The size of remnant lipoproteins is between ordinary large VLDL and small LDL. Usually only a few remnant lipoproteins are found in the blood, and they do not contribute very much at all to blood levels of cholesterol and triglyceride. In Type III hyperlipidemia, the numbers of remnant lipoproteins in the blood can be more than 50 times normal.

What are remnant lipoproteins, and where do they come from?

They actually are the “remnants” of VLDL and chylomicrons, from which most of the triglyceride has been removed by normal biochemical processes in the body. The remnant lipoproteins then rapidly go through further processing in the liver and are quickly removed from the bloodstream by the liver. (Some of the remnant lipoproteins are processed to become LDL,

but that is not important for understanding Type III hyperlipidemia.)

What is the key problem in Type III hyperlipidemia?

It is a failure of the liver to remove remnant lipoproteins from the bloodstream.

Why does the liver fail to remove remnant lipoproteins in this disorder?

In every case of Type III hyperlipidemia examined carefully thus far, the problem is not with the liver, but instead is with a protein which is ordinarily a part of VLDL, chylomicrons, and their remnants. This protein is called apolipoprotein E, or often just apoE. ApoE on the remnant lipoprotein “hooks and latches” the lipoprotein to the liver cell surface, so that the liver cell can dispose of the lipoprotein. In Type III hyperlipidemia, the patient has inherited (or sometimes newly developed) a mutated or bad gene for apoE. The mutated or bad apoE attaches weakly, or not at all, to the liver cell surface. Failing to attach, the remnant lipoproteins simply float past the liver cells, remaining in the bloodstream and accumulating to very high levels. Later we will discuss the genetic and inheritance of apoE and Type III hyperlipidemia.

How is Type III hyperlipidemia is recognized and diagnosed?

Type III hyperlipidemia should be suspected in a person who has cholesterol and triglyceride levels both above 350 mg/dl, and the cholesterol at least half as high as the triglyceride level. This fits with the idea that remnant lipoproteins have almost as much cholesterol as triglyceride. If there are several readings of cholesterol and triglyceride, we will often notice that they are highly variable – for example, the cholesterol may be over 500 at one time, but less than 300 on another reading. This variability fits with the fact that remnant lipoproteins come from triglyceride-rich lipoproteins (VLDL and chylomicrons) that also are different from week to week depending on diet and small changes in weight.

Lumps can grow beneath the skin at the elbows and knees, as well as other locations, if Type III hyperlipidemia gives very high cholesterol and triglyceride levels for a number of years. These lumps are called xanthomas (zan thoam' ahs). Other kinds of hyperlipidemia can also give xanthomas in the skin and tendons, but the xanthomas that jut out from elbows and knees belong only to Type III hyperlipidemia (these are called tuberous xanthomas, because they look like small potatoes beneath the skin). These xanthomas usually do not need to be removed by surgery. They will get smaller and disappear over one to three years if treatment is successful at lowering cholesterol and triglyceride levels to normal or almost normal. Another kind of xanthoma belonging only to Type III hyperlipidemia is yellow streaks in the creases of the palm in both hands. Doctors don't believe it when a fortune-teller tries to read your future in the lines of your palm, but if palmar xanthomas are seen there, then blockage of arteries could be in your future! All of the xanthomas, however, happen only when Type III hyperlipidemia is especially severe. Most people who get heart attacks, strokes, and blockage of leg arteries from Type III hyperlipidemia have never had xanthomas.

High and roughly equal levels of cholesterol and triglyceride, along with variability from one reading to the next, with or without xanthomas, can give strong suspicion for Type III hyperlipidemia, but a clear diagnosis requires a special blood test. The blood test uses a technique called ultracentrifugation to separate out remnant lipoproteins; cholesterol is then measured to determine the level of remnant lipoproteins in the blood. Another test called lipoprotein electrophoresis can also be helpful. A blood test to determine apoE genotype (see below for an explanation of this concept) is useful in borderline cases and also in cases where Type III has already been diagnosed by ultracentrifugation.

How is Type III hyperlipidemia treated?

Mostly, Type III hyperlipidemia is treated in the same ways that high cholesterol and triglyceride are treated in more common conditions. However, treatment of Type III hyperlipidemia is different in a few ways.

First, it is especially important to treat Type III hyperlipidemia well. It causes especially rapid growth of atherosclerotic plaques in arteries, which lead to heart attacks, strokes, and blockage of leg arteries.

Type III hyperlipidemia is a severe condition, but it usually responds well to treatment. In most patients, cholesterol and triglyceride levels can be lowered to normal levels (200 mg/dl or less for both cholesterol and triglyceride). Xanthomas will usually disappear. In almost all patients, an approach that combines diet, exercise, and medications will be needed.

Diet and exercise are important in the treatment of every kind of hyperlipidemia, but in Type III hyperlipidemia especially good results can be obtained with diet and exercise. As we said earlier, cholesterol and triglyceride vary a lot when a person has Type III hyperlipidemia, with high peaks and low valleys. With good diet and exercise, a person can spend most of the time in the valleys.

Dietary treatment should aim at lowering both cholesterol and triglyceride. It is important to reduce saturated fat and cholesterol in the diet, and also important to reduce carbohydrates that are rapidly absorbed from the gut into the bloodstream. You should not have “sugar drinks” such as soda or sweet tea at all. Bread and potatoes should be reduced, since these foods are rapidly absorbed. Eating bread or potatoes raise blood sugar levels almost as much as eating the same amount of pure sugar! While eating fruit is healthy, 4-5 servings of fruit or juice daily can raise triglyceride levels in a person with Type III hyperlipidemia.

Weight reduction and control are more important in Type III hyperlipidemia than in the usual treatment of high cholesterol. At times, we have seen Type III hyperlipidemia practically go away entirely when a patient lost 10 to 20 pounds. Even so, your doctor or other provider usually will prescribe medication for the cholesterol and triglyceride, instead of waiting for you to lose weight. The main reason is that very few people will actually lose 10 to 20 pounds. If you can do it, then you may need less medication afterward!

Two kinds of medication are especially good for Type III hyperlipidemia. These are fibrates and statins. The fibrate medications usually used in the U.S. are gemfibrozil (Lopid) and fenofibrate (Tricor). Either medication can be effective in lowering both cholesterol and triglyceride in this condition. Rarely, an older fibrate called clofibrate (Atromid-S) is used, if the others have caused side effects or have not worked. The statins include atorvastatin (Lipitor), fluvastatin (Lescol), lovastatin (Mevacor), pravastatin (Pravachol), and simvastatin (Zocor). The statins tend to lower cholesterol more than triglyceride in Type III hyperlipidemia.

It often happens that a single medication is not enough to reduce cholesterol and triglyceride to nearly normal levels in Type III hyperlipidemia. Your doctor or provider may choose to give both a fibrate and a statin together. This kind of combined therapy has a lot of benefit, but also has some special risks. Especially when gemfibrozil or clofibrate is used with a statin, patients can develop a severe muscle reaction, which is fatal in rare cases. Muscle aches (all over the body, not just in one place) or weakness can be warning signs. Despite the severity of this problem, it is unusual, and the benefit of combined treatment generally far outweighs the risk.

Sometimes your provider may choose to add niacin as a second drug, or even as a third drug, in combined therapy of Type III hyperlipidemia. Niacin has several side effects, especially flushing, but with careful instructions on how to take niacin, the side effects can usually be avoided. Niacin can add significantly to the treatment of both cholesterol and triglyceride.

Other treatments that can be added to help make the lipids better are fish oil or estrogen pills (Premarin, Estrace, and so on). One kind of medication is usually not used in Type III hyperlipidemia. This is medication which binds bile acids in the intestine, taken as cholestyramine (Questran), colestipol (Colestid), or colesevelam (WelChol).

How is Type III hyperlipidemia inherited? Will my children get it?

A block in the removal of remnant lipoproteins from the bloodstream, due to weak or no attachment of apoE to the liver cell surface, is the cause of Type III hyperlipidemia. However, understanding exactly how this happens is a fairly complicated story, which we will now explore. This will allow us to estimate the likelihood that a son or daughter can inherit Type III hyperlipidemia from a parent.

A brief review of genetics is necessary. The word “gene” refers to the location of a piece of DNA in the chromosomes that specifies a protein – for example, the protein that accounts for eye color. Thus we speak of a gene for eye color. The exact pattern of DNA in a gene (in other words, at a particular chromosomal location) is called an “allele.” There is an allele that gives a protein making brown eye color and another allele giving a protein making blue eye color (there may be additional alleles giving varying shades of color, but blue and brown are enough for this example). Each of us has two alleles for every gene, one allele inherited from mother and the other inherited from father. In the example of eye color, you must inherit two “blue” alleles to have blue eyes. If you inherit two “brown” alleles or one “brown” and one “blue,” then your eye color will be brown.

Of all the patterns of DNA – alleles – that occur at the apoE gene location, there are just 3 that are found in more than 99% of all people. These alleles are named apoE2, apoE3, and apoE4. (The fact that there is no apoE1 allele is due to the history of how the alleles were discovered; “apoE1” appeared in a certain laboratory test, but was found not to have its own allele.)

When researchers first discovered that Type III hyperlipidemia was related to apoE, they found that 80-90% of all patients with Type III have inherited apoE2 from both mother and father – that is, they have 2 copies of the apoE2 allele. Sometimes, this condition is abbreviated apoE2/apoE2, or simply apoE2/2. Further research showed that apoE2 attaches weakly to the liver cell surface. So apoE2 is a key cause of the problem! However, if only half of the apoE on your remnant lipoproteins is the weak apoE2, and the remaining half is apoE3 or apoE4, then the remnant lipoproteins still attach to liver cells and are cleared away practically normally. Thus it appeared that the mystery of Type III hyperlipidemia was solved.

Even this explanation was too simple, however. Type III hyperlipidemia is quite rare – about 1 out of 5,000 people around the world have it. Yet the apoE2/2 condition is found in 1 out of 100 people. If you do the math (5,000 divided by 100), you can see that only 1 out of 50 people who have apoE2/2 actually get Type III hyperlipidemia.

How does this happen? Certain cases of Type III hyperlipidemia help us learn more. Some people were doing just fine with apoE2/2, but developed Type III when their thyroid gland became diseased and made too little thyroid hormone. When these people took thyroid hormone to replace the natural hormone, the remnant lipoproteins of Type III hyperlipidemia were cleared away, and their cholesterol and triglyceride levels became normal. So apoE2/2 plus a low thyroid condition caused Type III, but in these people apoE2/2 by itself did not cause Type III. In other cases, people with apoE2/2 developed Type III hyperlipidemia when they became diabetic. Treatment of the diabetes with insulin or with pills tended to make the cholesterol and triglyceride levels better, but not entirely normal. In yet another group of people with apoE2/2, Type III hyperlipidemia appeared only after these people became overweight.

These cases illustrate the idea that, in order to get Type III hyperlipidemia, you need apoE2/2 plus some other condition. People with apoE2/2 are often barely getting by, just barely able to attach remnant lipoproteins to the liver cell surface fast enough to clear away the remnant lipoproteins. If some other condition comes along, causing more remnant lipoproteins to be made in the body, then the system becomes overloaded, and the number of these lipoproteins in the blood goes up 50 times or more higher than normal – this makes Type III hyperlipidemia happen. But the cases mentioned above are very rare. For most people who have Type III hyperlipidemia, the “other condition” is neither low thyroid, nor diabetes, nor entirely overweight (weight loss almost always helps, however!). In most patients, the “other condition” is assumed to be some combination of other unknown genes and their alleles. Interestingly, as rare as Type III hyperlipidemia is among adults, it is much more rare in children. This means that if a person is born with the genetic makeup that will eventually cause Type III, it still usually does not occur until the person reaches adulthood.

That is almost the complete story of the causation of Type III hyperlipidemia, but not quite. You

may recall that 80-90% of patients with Type III have apoE2/2. What about the other 10-20%? You may also recall that more than 99% of all the apoE alleles are either apoE2, apoE3, or apoE4, but there are other mutant (bad) apoE alleles in a tiny fraction of people. The other 10-20% of Type III hyperlipidemia cases occur in those very few people who have the other mutant apoE alleles. With extreme rarity, a person may not make the apoE protein at all – that is, the mutant allele is so bad that no protein is made from it. In other cases, the mutant alleles act like apoE2. To get Type III hyperlipidemia, these people must inherit mutant apoE from one parent and either mutant apoE or apoE2 from the other parent. However, there are also some very rare “dominant” mutant alleles of apoE. These “dominant” alleles are especially bad, since they somehow cancel the ability of good apoE3 or apoE4 to attach to the liver cell surface.

Now we can estimate the likelihood that a son or daughter would inherit Type III hyperlipidemia, if one parent has it. The key to making such an estimate is to know whether the parent with Type III hyperlipidemia has apoE2/2 or not. (This also applies to prospective parents, that is, people who want to consider having children in the future.) If the person with Type III hyperlipidemia has apoE2/2, then it is extremely unlikely that a child will get the same severe Type III hyperlipidemia, for several reasons. First, think about the fact that the child would have to receive one of his or her apoE2 alleles from the patient’s spouse. Of all the apoE alleles in the world, about 7% are apoE2. So there is only a 7% chance, or one in 14, that a child would receive the second dose of apoE2 from the other parent. But that is not all. Remember that some other condition, in addition to apoE2/2, is also needed to cause Type III hyperlipidemia. The likelihood that a child would experience the other condition is also small, leaving us with an estimate that a child might have less than 1% chance of Type III hyperlipidemia.

What if the parent with Type III hyperlipidemia does not have apoE2/2? This is a more complicated situation, which actually gives a higher likelihood that a child would develop Type III hyperlipidemia. The problem is that some cases of Type III without apoE2/2 have the “dominant” mutant apoE allele described above. In this case, the child can inherit a strong tendency toward high levels of remnant lipoproteins simply by getting the dominant mutant apoE. Furthermore, in some dominant cases, Type III appears to develop without any “other condition” as is needed for inheritance in apoE2/2 cases. Therefore, in a few families with a dominant mutant apoE allele, Type III hyperlipidemia can be passed along from grandparent to parent to child, and so on, affecting about half the children of every parent who carries the allele.

A blood test is available to determine the apoE genotype of any person. This test will tell if you have one or two alleles from among these three: apoE2, apoE3, apoE4. The result might be apoE2/2 (most common in Type III), apoE3/3 (most common in everybody else), apoE3/4, or any other combination. However, this test will not determine if you have a very rare mutant apoE allele. In this test, the very rare mutant will look like one of the three mentioned. The diagnosis of a dominant mutant apoE allele can be made if Type III hyperlipidemia shows dominant inheritance in a family (grandparent to parent to child). In practicality, it is not necessary to determine the genetic sequence of the bad apoE allele in every family with Type III hyperlipidemia, since the level of treatment and attention given to family members simply depends upon two key considerations: (1) whether or not apoE2/2 is involved, and (2) if apoE2/2 is not involved, then whether a dominant inheritance pattern is found in the family.

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