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If triglycerides matter, why do they matter?

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ABSTRACT

While there is no dispute that hypercholesterolemia increases the risk of cardiovascular disease, controversy as the importance of hypertriglyceridemia persists. Much of this relates to the fact that hypertriglyceridemia is not a single disorder but rather is a collection of disorders in which elevation of plasma triglycerides is due to the accumulation of different triglyceride-rich lipoproteins, some of which, such as remnant lipoprotein particles are ferociously atherogenic whereas others, such as intact chylomicrons, are not but do increase the risk of pancreatitis. Based on just the major lipoprotein lipids-cholesterol and triglycerides-the 6 major apoB dsylipoproteinemias cannot be separated and each identified. The apoB algorithm, which is based on total cholesterol, triglycerides and apoB, all three of which can be measured inexpensively in standard clinical laboratories, for the first time, allows all the specific apoB dyslipoproteinemias to be easily and accurately identified. By incorporating apoB into clinical care, we move from the lipid to the lipoprotein era with more precise identification of those who require pharmacological therapy and more rational and precise use of pharmacological agents to reduce their risk of cardiovascular disease.

1. Introduction

Contrary to conventional wisdom, hypertriglyceridemia is much more common than hypercholesterolemia in patients with vascular disease.[1] Moreover, recent observational studies and studies using Mendelian randomization confirm triglycerides are an important risk factor for cardiovascular disease.[2] Thus, it would seem there should be aggressive treatment targets for hypertriglyceridemia just as there are aggressive treatment targets for hypercholesterolemia. Unfortunately, notwithstanding all the circumstantial evidence that triglycerides (TG) should matter, there is no hard evidence that they do. That is, to date, there is no evidence from randomized clinical trial evidence that pharmacological lowering of TG reduces clinical events. This failure suggests that we should re-evaluate why triglycerides might matter.

I will suggest the answer is that some forms of hypertriglyceridemia do matter while others do not and therefore we should learn how to separate one from the other and treat those that do and put aside those that do not. In other words, we should learn that low-density lipoprotein (LDL) always matters, that triglycerides matter only sometimes, and that other times, which is to say most of the time, TG matter because they point us back to LDL.

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2. Hypertriglyceridemia: a heterogeneous group of disorders

Hypertriglyceridemia is not a diagnosis because hypertriglyceridemia is not a single, simple, discrete, homogeneous entity. On the contrary, hypertriglyceridemia is a collection of different disorders with different causes, different risks and different treatments.[3] Table 1 provides a list of the hypertriglyceridemic phenotypes and their associated vascular risk. This phenotypic designation is based on which type of TG-rich particle is present: chylomicrons versus chylomicron and very low-density (VLDL) particles versus chylomicron and VLDL remnant particles versus VLDL particles with or without increased number of LDL particles (Fig. 1). Patients with markedly elevated TG levels due to massive accumulation of chylomicron particles or chylomicron plus VLDL particles are not at increased risk of vascular disease. Rather they are at increased risk of pancreatitis.[4] By contrast, hypertriglyceridemia due to chylomicron and VLDL remnant lipoprotein particles are at high risk of cardiovascular disease and do require appropriate pharmacological therapy.[5] (Fig. 2) Further, there are two phenotypes in which hypertriglyceridemia is due to elevated VLDL: in one, VLDL is increased but a normal number of apoB particles are present (Fig. 3A) and cardiovascular risk is not markedly elevated whereas in the other, VLDL is increased and so also is the number of apoB particles due primarily to a marked increase in the number of LDL particles (Fig. 3B). In this phenotype, vascular risk is substantially increased but the real culprits are the LDL particles not the VLDL particles.[1]

3. The ApoB families of lipoprotein particles

Presently, clinical diagnosis is based on the plasma and lipoprotein lipids: plasma TG, total cholesterol (TC), LDL cholesterol (LDL-C), non-HDL cholesterol (non-HDL-C), and high-density lipoprotein cholesterol (HDL-C). With just this information, it is not possible to differentiate and therefore accurately diagnose the apoB atherogenic dyslipoproteinemias. However, with only TC, TG, and apoB, all of the different phenotypes can be easily and instantly distinguished.[6] The apoB app is free and is available for both Apple and Android devices.

The apoB diagnostic algorithm is based on the differing but characteristic compositions of the various apoB lipoprotein particles (Fig. 1).[3] To summarize, there are three families of lipoprotein particles: the apoB48 lipoprotein particles that transport the cholesterol and TG that was ingested in the diet and absorbed within the intestine to storage and utilization sites within the body and the apoB100 lipoprotein particles that transport excess TG and cholesterol from the liver to other tissues within the body; and the apoA-1 or HDL particles that-amongst other things-remove excess cholesterol from peripheral tissues and via a complex series of events and transport it back to the liver.[3]

We will focus on the two apoB families (Fig. 1). Each apoB lipoprotein particle is encircled by one molecule of apoB: apoB48 in the case of the intestinal apoB particles and apoB100 in the case of the hepatic apoB particles. Therefore, the plasma apoB48 is equal to the total number of intestinal apoB particles whereas the plasma apoB100 is equal to the total number of hepatic apoB particles. There are two apoB48 particles: chylomicrons, the particles secreted by the intestinal cells that transport dietary TG to adipose tissue and chylomicron remnants, the chylomicron particles that are released by adipocytes after much of their TG has been removed and that are rapidly removed by the liver. Similarly, there are also two principal forms of the apoB100 particles: VLDL particles, the TG-rich particles secreted by the liver and LDL particles, the cholesterol-rich particles that are, for the most part, products of the metabolism of VLDL particles. In contrast to chylomicron remnants, which are normally removed within a few minutes from the circulation, LDL particles persist for a prolonged period, on average 3–4 days, whereas the half-life of VLDL particles is 3–4 h. Accordingly, there are 9 times as many LDL particles as VLDL particles and this relation holds even in patients whose hypertriglyceridemia is due to an increased number of VLDL particles (Fig. 2). Similarly, even at peak postprandial periods there are 9 times as many VLDL particles as chylomicron and chylomicron particles. Therefore, plasma apoB is determined by the LDL apoB: that is, because LDL particles account for more than 90% of the total number of apoB particles, plasma apoB is, effectively, a measure of LDL apoB. This is key.

However, there is one exception and one caveat to this general rule. The exception is remnant lipoprotein disorder, the apoB dyslipoproteinemia, which is characterized by markedly increased numbers of remnant chylomicron and VLDL particles (Fig. 2).[5] In this syndrome, which is associated with extreme cardiovascular risk, remnants can account for up to 40% of total apoB particles.[3] The caveat is that as TG levels due to increased VLDL rise above 300 mg/dl, the proportion of VLDL to LDL particles does change somewhat, but this is not marked and LDL particles continue to account for the great majority of apoB particles.

Table 1 – Cardiovascular risk in the hypertriglyceridemic phenotypes.

Phenotype	Vascular risk
↑ Chylomicrons	→
↑ Chylomicrons + VLDL	→
↑ Chylomicrons + VLDL remnants	↑↑↑
↑ VLDL and Normo-apoB	→
↑ VLDL and Hyper-apoB	↑↑↑

4. The apoB diagnostic algorithm

Based on the known composition of all the different apoB lipoprotein particles, we have developed a simple algorithm using TC, TG and apoB to differentiate all the apoB dyslipoproteinemias.[6] TC, TG and apoB can be determined with the equipment available in any modern clinical chemistry laboratory. Measuring apoB has not yet become part of conventional clinical care. Yet the measurement of apoB is standardized, automated, and inexpensive (<$5 American).[7]