Bring in the New with the Old: Measuring LDL Cholesterol

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In March 2010 the cholesterol results from the Canadian Health Measures Survey were released. Results report that 30 per cent of adult Canadians had unhealthy levels of HDL cholesterol, while 36 per cent had unhealthy levels of LDL cholesterol. LDL increased with age, but peaked at 43 per cent among adults aged 40 to 59 (Statistics Canada 2010). The numbers are somewhat surprising, considering

- this age group makes up a large portion of the working population
- people generally develop risk for heart disease after the age of 60 and
- a high LDL is a known risk for cardiovascular disease (CVD) (Yamada et al. 2005).

This article provides background information on cholesterol—more specifically LDL—and highlights associated screening measures.

Cholesterol

Cholesterol is not just a waxy substance, but also an important biological molecule that plays a role in membrane structure. It is a precursor for the synthesis of steroid hormones including vitamin D and bile acids. There are two sources of cholesterol: 1) exogenous or dietary, and 2) endogenous or new because it is synthesized by the liver enzyme HMG-CoA reductase. Both sources are transported through the circulation in lipoprotein particles because cholesterol is insoluble in blood. Cholesterol is then stored in the cell in the form of a cholesterol ester (CE). Our bodies are capable of synthesizing 85 per cent of our cholesterol needs which is between one to two grams a day and the other 15 per cent of cholesterol comes from our dietary intake (Genest 1990).

Lipoproteins and Apolipoproteins

Lipoproteins are specialized proteins within a complex spherical bilayer of phospholipids and a core of CE, the hydrophobic form of cholesterol, and triglycerides (TG). The TGs are composed of one glycerol and three fatty acids (FA). The proteins are referred to as apolipoproteins (Apo) and they act as ligands for cellular receptors and as well as cofactors for enzymes related to the lipoprotein metabolism. Apolipoproteins are classified in families according to size, distribution in lipoproteins and other characteristics (see Table 1).

Table 1. Examples of Apolipoproteins

Apolipoprotein	Important Features
Apo A-I	Main protein in HDL; activates LCAT
Apo B100	Main protein in LDL; binds to LDL receptor
Apo C-II	Important in the composition of chylomicrons and VLDL; activates lipoprotein lipase
Apo E	Important in chylomicrons, VLDL and IDL, allowing the binding of these lipoproteins to the hepatocytes

Types of Lipoproteins

There are five types of lipoproteins and their lifecycles can be broken down into three stages: nascent, mature and remnant. The particle classes of each of the chylomicrons (CM), very-low-density lipoproteins (VLDL), and intermediate density protein (IDL) all typically carry one molecule of Apo B, Apo C and Apo E, whereas the low-density lipoproteins (LDL) carry one molecule of Apo B and the high-density lipoproteins (HDL) carry one molecule of Apo A. HDL and LDL are often the focus of the literature because of the common shorthand descriptors: good and bad cholesterol. This has been influenced by therapy targets, which focus primarily on lowering LDL and increasing HDL cholesterol (Yamada et al. 2005). These shorthand terms do not fully explain their roles in lipid metabolism and potentially create confusion with the public when they receive a lipid profile that also measures other lipoproteins.

A conventional lipid screening typically includes fasting serum measures of total cholesterol (TC), HDL and triglycerides (TG) with calculated values of LDL and the ratio of TC:HDL. This ratio of TC:HDL is referred to as the cardiac risk ratio because a high ratio has positive predictability of CVD development (Shaw et al. 2003). A review of the lipoprotein pathways will illustrate why a lipid profile presently includes specific lipoproteins and not others.

Endogenous Pathway—LDL, VLDL, and IDL

LDL is composed of 60 to 70 per cent cholesterol and is responsible for the endogenous pathway that delivers lipids from the liver to the cells. The biological half-life of an LDL particle is at least nine times longer than that of a VLDL particle and, therefore, there are always nine times more LDL particles than VLDL particles. As LDL is taken up by receptors, free cholesterol is released and accumulates within the cells. TGs and CEs are generated by the liver and packaged into the VLDL particles and then released into circulation. VLDL is TG rich and is processed by the lipase enzyme (LPL) in the tissues to release fatty acids and glycerol. The free fatty acids (FFA) are taken up by muscle cells for energy or by the adipose cells for storage. Once processed by LPL, the VLDL becomes a VLDL remnant (VLDLr). The liver via the LDL receptor takes up the majority of the VLDLr, and the remaining remnant particles become IDL—an intermediate and a smaller, denser lipoprotein than VLDL.

Small Particles of LDL

The liver reabsorbs some of the IDL particles. Other IDL particles are hydrolyzed by hepatic-triglyceride lipase (H-TGL) to form a version of LDL—a smaller, denser particle than IDL. The smaller and denser these particles are, the more likely they contribute to the formation of atherosclerotic plaque in the presence of other factors, such as chronic inflammation. This is because these smaller particles referred to as LDL Pattern B are more easily able to penetrate the endothelium. The large fluffy LDLs are referred to as Pattern A. In the last decade the research has suggested that the correlation between Pattern B and coronary heart disease (CHD) is stronger than that between the LDL number measured in the standard lipid profile

(2000). Tests to measure these LDL subtype patterns are more expensive and not widely available, so the common lipid profile test has continued to be the default[*].

Exogenous Pathway—Chylomicrons

Less talked about are the chylomicrons (CM), which are assembled in the intestinal mucosa as a means to transport dietary cholesterol and TG to the rest of the body. CMs are the molecules formed to mobilize exogenous lipids. They circulate through the intestinal lymphatic system and in the blood. The circulating CMs interact at the level of the capillaries in adipose tissue and muscle cells. CMs release TG to the adipose tissue to be stored and available for the body's energy needs. Some of the CM components are "repackaged" into other lipoproteins and the remaining chylomicron remnant (CMr) particles are removed from the plasma by way of CMr receptors present on the liver. Specifically, this CMr clearance is mediated by Apo E receptor ligand. Therefore, genetic deficiency of Apo E leads to a large accumulation of CE-rich CMr and IDL in the bloodstream.

Reverse Cholesterol Transport—HDL

HDL is the key lipoprotein involved in reverse cholesterol transport and the transfer of CE between lipoproteins. This pathway removes cholesterol, minimizing the buildup of LDL from the tissues and returns it to the liver (Genest 1990). HDL is the smallest and has the highest density of the lipoprotein particles and can be differentiated into subclasses of particles: HDL_2 and HDL_3. Several mechanisms and complementary pathways have been proposed by which the HDL delivers and returns CE to the liver.

Apo A-I is the major protein present in the plasma of HDL and contributes to the reverse cholesterol transport by aiding in the removal of free cholesterol from the peripheral tissues to the liver. This occurs through the interaction with a binding protein in the plasma membrane and forms a nascent HDL (Tall 2003). The free cholesterol in HDL is then esterified by lecithin cholesterol acyltransferase (LCAT), and Apo A-I acts as a cofactor for this enzyme and this results in the delivery of CE from lipoproteins to the liver and other tissues by selective uptake *(*Connelly et al. 2004)

Cardiovascular Risk

It is well established in the published literature that elevated levels of Apo A-I and HDL are correlated with decreased risk for CVD, conferring a protective effect. It is also appreciated that LDL specifically Pattern B, VLDL, IDL and their remnant particles are highly atherogenic and contribute to an increased risk for heart disease. Recently the literature has focused on Apo B since it is a measure of the total number of atherogenic particles. Many studies including the *Apolipoprotein-Related Mortality Risk Study* (AMORIS) show that Apo B is a better marker for vascular disease risk. In this study Apo B and Apo A-I were highly significant at any concentration of total cholesterol and TG, regardless of sex and age. This is not the case with LDL, which was only marginally significant in men and not in women or older patients (Thompson et al. 2006).

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[*] It is difficult and unwise to replace a conventional test when both doctors and patients have a lot of experience with it. It is unwise for many reasons to abandon a tried-and-true method for a new, less expensive approach that really is geared only to those with CAD.

Targeted Values for Lowering LDL Varies

A lipid profile can be used in primary prevention for screening individuals who do not have any known risk factors for coronary artery disease (CAD). Their LDL levels would be targeted at the standard reference range yet optimal levels would be lower. The reference range associated with healthy limits for LDL is 3.2 to 3.4 mmol/L. If an individual presents with risk factors such as obesity and hypertension then their target LDL will be below 2.6 mmol/L at the optimal level (NCEP 2010). Adding genetic history or previous heart attack to these other risk factors will result in the highest risk of CAD and the individual will need to be more vigilant and keep LDL levels under 1.8 mmol/L. This may be achieved through diet and exercise, but more likely through pharmacological intervention. The treatment of elevated LDL clearly is ever-changing as research continually hones our understanding of what lowers LDL; there is no single “norm” anymore.

In summary the most common lipid profile test has been the default because other tests are expensive, not widely available, and not warranted for first time screening purposes. However, given the importance that has been assigned to LDL cholesterol-lowering treatment, the addition of Apo A-I and Apo B could provide more specific outcomes associated with changes in lipid metabolism particularly where genetics are known. In fact, these new tests are important because the future may show that LDL Pattern B will be the priority for measurement in individuals who present with CVD risk factors. Lipoproteins levels, when interpreted in the appropriate context, are important markers of metabolic problems, including low LDL receptor activity.

References available on request.