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Improving a Patient's CVD Risk Assessment—Updating the Interpretation of the Lipid Profile

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Abstract

The lipid profile remains an important laboratory assessment to prevent cardiovascular disease. Interpretation of the non-fasting lipid profile has significantly changed based on new information concerning the pathogenesis of atherosclerosis. In particular, the assessment of risk from cholesterol containing particles following triglyceride metabolism (termed remnant cholesterol) can now be done from a lipid profile. In addition, non-HDL cholesterol as calculated from the lipid profile will provide a complete assessment of total circulating cholesterol containing particles. Furthermore, the formula for measurement of LDL cholesterol from a lipid profile has now been revised so that triglyceride levels exert less interference. Finally, the old concept that the "higher the HDL-c, the better" is no longer tenable. New data indicate that the optimal high density lipoprotein level is below 100 mg/dl for both male and female patients. Correct interpretation of the lipid profile will optimize anti-atherosclerotic therapy and reduce the number one cause of death in the United States.

Keywords

Lipid Profile, Atherosclerotic Risk, Cardiovascular Disease, High Density Lipoprotein, Low Density Lipoprotein

1. Introduction

Since cardiovascular disease (CVD) is the number one cause of death in the United States, assessing each patient's risk is critical for determining effective therapy. When either internet risk calculators (IRC) and/or coronary artery calcium scan-

ning (CAC) are used for this purpose, only population estimates of risk are provided. Unfortunately, each of these approaches has its limitations. For IRC, poor prediction occurs in various population subgroups (e.g., young men and women) whereas for CAC, the limitation is the inability to quantitate non-calcified atherosclerotic plaque that can rupture [1] [2]. Fortunately, correct interpretation of each individual's lipid profile can greatly increase the precise estimation of that individual's CVD risk. The higher the risk, the more aggressive the therapy should be. The individual's lipid profile, when appropriately interpreted, can provide the physician with a unique assessment of patient risk. The following discussion provides an update of current interpretation of the standard components of the lipid profile plus the addition of two new parameters shown to be valid additions to risk assessment.

2. Total Cholesterol

This parameter includes all cholesterol that is contained in circulating lipid particles. Historically, it was used as a measure of cardiovascular risk. Problematically, total cholesterol includes both anti-atherogenic high density lipoprotein cholesterol (HDL-c) and atherogenic apo B containing low density lipoprotein (LDL-c) particles. Therefore, it can be elevated because the HDL-c is elevated (beneficial) or the LDL-c is elevated (detrimental). Its primary use now is in calculating other risk parameters such as total atherosclerotic cholesterol (Tot-athero-c), remnant cholesterol (Rem-c), and low-density lipoprotein cholesterol (LDL-c).

3. HDL Cholesterol

This lipid parameter is often designated as the "good cholesterol." This term refers to the fact that HDL-c accepts cholesterol from tissue macrophages and transports it either to the liver via SB-1 hepatic receptors or to LDL-c for disposal via hepatic LDL-c receptors (termed reverse cholesterol transport (RCT). More importantly, the concentration of HDL-c does not always indicate the degree of anti-atherogenesis. In fact, the optimal level of HDL-c for RCT is approximately 70 mg/dl in men and 90 mg/dl in women [3]. Therefore, the beneficial effects of HDL-c are not optimally predicted by the magnitude of its concentration but instead by its rate of activity to accept cholesterol from peripheral tissue macrophages [4] [5]. Therefore, the ratio of total cholesterol to HDL-c, when included in a lipid profile, should be ignored.

4. Triglycerides

Triglycerides are not lipid particles per se but molecules with a backbone of glycerol to which is attached three carboxylic acid side chains. Multiple triglyceride molecules are incorporated into both chylomicron particles and very low density lipoproteins (VLDL). Although many studies have observed a positive correlation between triglycerides and cardiovascular risk, triglycerides are not considered atherogenic per se but are associated with atherogenic remnant particles. Triglycerides

are used to calculate the circulating level of LDL-c (Total cholesterol minus [HDL-c + TG/5]). More recently, a new formula has been recommended. Instead of assuming a fixed factor for triglycerides/5, it applies an adjustable factor for the TG: VLDL-c ratio based on triglyceride and non–HDL-c concentrations [6]. LDL-c may also be directly assayed, especially if the TG concentration exceeds 400 mg/dl. The non-fasting triglyceride level is used to calculate remnant cholesterol (Tot Chol minus [HDL-c + LDL-c]). Depending on the duration of the fast, the elevation in triglyceride for many hours post meal may not be observed in the fasting state. This application is an especially important part of assessing CVD risk since remnant cholesterol may be more atherogenic than LDL-c [7] [8].

5. LDL Cholesterol

This particle remains after the majority of triglycerides are removed from VLDL by lipoprotein lipase. It contains a very high concentration of cholesterol. Prior to hepatic removal, it may accept additional cholesterol from HDL-c in exchange for triglycerides when activated by cholesterol ester transfer protein. In the circulation, it may enter the sub-endothelial vascular space, become oxidized, and be taken up by tissue macrophages. It is a principal atherogenic particle and the primary cause of cardiovascular events in hypercholesterolemic patients [9]. Very high levels (greater than 1000 mg/dl) may be measured in patients with chronic obstructive liver disease due to the presence of lipoprotein X which co-migrates with LDL in the LDL-c assay [10]. However, this particle is not atherogenic, so its identification is important. Studies of subfractions of LDL particles have shown that small LDL-c particles are more atherogenic than large particles and move more readily into the arterial subendothelial space. Although a separate analysis of LDL-c particle size can be obtained, a lipid profile provides an estimation of LDL-c particle size. The greater the triglyceride level, the smaller the average size of LDL-c particles [11] [12]. Finally, the Lp(a) particle contains an LDL particle and in addition, contains a variable number of amino acid side chains called kringles. Therefore, when an assay for LDL-c is performed, the Lp(a) particle may also be measured by a variable amount, providing an inaccurate assessment of LDL-c concentration. One reason for statin treatment non-responsiveness in lowering LDL-c is its partial inclusion in the LDL-c assay.

6. Total Atherogenic Particles

Since measurement of LDL-c does not include other atherogenic particles (e.g., chylomicron remnants, very low density lipoproteins (VLDL), and intermediate density lipoproteins [IDL]), a measurement of these parameters is important in the assessment of cardiovascular risk. This can be achieved by an additional assay of total lipoprotein apo B concentration, which provides the total number of atherogenic particles. However, a lipid profile can provide an estimation of total atherogenic particles based on their cholesterol content (Tot-chol minus HDL-c cholesterol). This measurement may be more predictive of future cardiovascular

events than LDL-c [13].

7. Remnant Particles

Recent studies suggest that remnant atherogenic particles may be more predictive of future cardiovascular events than LDL-c particle concentration, particularly in the non-fasting state [13]. This parameter is calculated from the lipid profile (Totchol minus (HDL-c + LDL-c). It represents the residual cholesterol in chylomicrons, VLDL, and IDL. On a particle per particle basis, a chylomicron remnant particle has eight times more cholesterol than an LDL-c particle [14]. In the non-fasting state, an individual with elevated (greater than 30 mg/dl) remnant cholesterol is exposed to this elevated atherogenic parameter 24 hours/day. In the past, patients were instructed to obtain a lipid profile in the fasting state. In fact, the only component of the lipid profile that changes in the non-fasting state is the level of triglycerides [15]. Most cardiovascular guidelines now endorse the use of non-fasting samples for an initial lipid profile [16].

8. Summary

A lipid profile, when carefully analyzed, can provide a wealth of cardiovascular risk information, especially considering its low cost ($50 from Quest Diagnostics Inc.). Each component of the lipid profile provides important, yet separate insight into cardiovascular risk (**Table 1**). Calculation of remnant lipoprotein concentration should always be done since it provides an independent and important assessment of patient risk. Additional procedures, including measurement of Lipoprotein (a) and high sensitivity C-reactive protein testing will improve the physician's assessment of a patient's CVD risk and guide the physician toward appropriate cardiovascular disease preventive therapy.

Table 1. Parameters of importance relative to the lipid profile.

Parameter	Calculation	Importance
Total Cholesterol	Not required	Used to calculate other important parameters
High Density Lipoprotein Cholesterol	Not required	Responsible for Reverse Cholesterol Transport
Triglycerides	Not required	Not atherogenic per se, but highly correlated with atherosclerotic events
Low Density Lipoprotein Cholesterol	Tot Chol – (HDL-c + TG/5). An alternative formula may be used	A highly atherogenic particle. Can be assayed directly at additional cost.
Total Atherogenic Particles	Tot Chol minus HDL-c	Includes all atherogenic particles
Remnant Particles	Tot Chol minus (HDL-c + LDL-c)	Maybe more atherogenic than LDL-c
Lipoprotein X	Measured in the LDL assay	Not atherogenic-observed in biliary obstruction
Lp(a)	Assay Separately	Very Atherogenic

The reader should consider the limitations of this article. Depending on the

patient's clinical condition, additional testing in addition to a lipid profile may be warranted. For example, the patient's status of inflammation may be assessed with a high sensitivity C-reactive protein measurement. Testing for Apo-B will provide additional assessment of atherogenic particles. Finally, ultracentrifugation or magnetic resonance imaging of LDL-c will indicate the number of large (less atherogenic) compared with small (very atherogenic) LDL-c particles. In addition, performing a lipid profile measurement more frequently than once/year may be necessary if hypolipidemic treatment changes or co-morbidities change such as worsening diabetes or hypertension.

What should the primary caregiver do if the lipid profile demonstrates increased risk beyond that suggested by the LDL-c concentration? Our suggested approach is to proceed with the next step that you would not normally take in your practice including one or more of the following actions: 1) order a coronary artery calcium scan to better define the risk, 2) add 10 mg/day of ezetimibe to a statin to reduce inflammation and LDL-c, 3) prescribe a PCSK-9 inhibitor to lower LDL-c and Lp(a), 4) reemphasize the effectiveness of a low cholesterol diet, 5) prescribe bempedoic acid if the patient is statin intolerant, and 6) lower the LDL-c concentration to the next lowest recommended guideline level. In other words, the physician should be much more aggressive in reducing the patient's cardiovascular risk.

Conflicts of Interest

None of the authors has a conflict of interest in the submission of this manuscript.

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