LDL subfractions Analysis in Pro-atherogenic Dyslipidemia

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Abstract

Background Early recognition of pro-atherogenic risk factors is important for prevention and treatment of atherosclerotic cardiovascular disease (CVD). The National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) guidelines identified LDL cholesterol (LDL-C) as the primary target for CAD therapy and risk assessment. Although the association between elevated levels of LDL cholesterol and increased risk of cardiovascular disease (CVD) is well established, recent data reveal that a relative high proportion of individuals develop atherosclerosis and heart disease in spite of having LDL cholesterol levels in the normal by traditional guidelines. Of these individuals with elevated LDL cholesterol remain disease free.

Objective Demonstrate the benefit of measuring the atherogenic LDL subfractions with the comprehensive analysis on the Lipoprint LDL system and assist clinicians in identifying, stratifying and customizing treatment for those at risk.

Methods Lipid profiles for a total of 273 recruited subjects were determined by testing their total cholesterol, triglycerides, LDL-C and HDL-C using standard clinical methods. Subjects were segregated into two groups, "normal" and "pro-atherogenic" according to the ATP III guidelines reference ranges (Desirable: 130 mg/dL, Borderline: 140 – 159 mg/dL, High: ≥ 160 mg/dL).

Lipoprotein LDL Profile Versus Traditional Lipid Profile

The samples were analyzed for LDL-2 (small dense LDL cholesterol), LDL-3 to LDL-7 (small dense LDL) and HDL in both, the “normal” and “pro-atherogenic” subgroups. The Lipoprint LDL system and LDL Subfractions kit (Quantimetrix Corporation, Redondo Beach, CA) was used to measure the cholesterol profiles for each lipoprotein subfraction. The Lipoprint LDL system offers a new method to calculate the corresponding NMR LDL particle number and LCL-C is no longer a target for treatment in secondary prevention.

The Lipoprint LDL profiles were compared to the traditional lipid profile methods that measure all the LDL subfractions. The Lipoprint LDL system and LDL Subfractions kit (Quantimetrix Corporation, Redondo Beach, CA) was used to measure the cholesterol profiles for each lipoprotein subfraction. The Lipoprint LDL system and LDL Subfractions kit (Quantimetrix Corporation, Redondo Beach, CA) was used to measure the cholesterol profiles for each lipoprotein subfraction.

Results The results were compared to the traditional lipid profile methods that measure all the LDL subfractions. The Lipoprint LDL system and LDL Subfractions kit (Quantimetrix Corporation, Redondo Beach, CA) was used to measure the cholesterol profiles for each lipoprotein subfraction.

Conclusions Clinical studies identify small dense LDL, VLDL remnants and IDL density lipoprotein (IDL) and small dense LDL as well as the subclasses varying in density, particle size, chemical composition, function and atherogenic potential. LDL subfractions include the atherogenic triglyceride enriched very-low density lipoprotein (VLDL), intermediate density lipoprotein (IDL) and small dense LDL (sLDL). These LDL subclasses have been shown to be more closely associated with CVD risk than traditional lipid assessment methods that measure all the LDL subfractions.

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**Discussion**

Coronary artery disease (CAD) continues to be the leading cause of death in most of the developed countries and much of the developing world in spite of worse risks and increased awareness of treatment of individuals at risk. The role of lipids and lipoproteins in atherogenesis has been demonstrated by numerous studies but the methods for assessing CAD have continued to be the subject of much debate. In November 2013, the ACC/AHA Task Force released new guidelines and a new CVD risk calculator based on data from randomized control trials. The risk calculator weighs heavily on non-risk lipid factors reducing the role of LDL-C and other lipid measurements as risk factors.

Recent clinical studies suggest that blood cholesterol and LDL-C levels as currently defined do not accurately reflect the actual risk of CAD among those individuals that develop CAD have the same levels as those that do not develop CAD. These findings suggest that dyslipidemia, as currently defined, may not be a good indicator of CAD risk. The most common lipid disorder associated with CAD is a pro-atherogenic dyslipidemia characterized by the presence of highly atherogenic small dense LDL particles and intermediate density lipoproteins and VLDL remnant particles. Recent studies have shown that the number of individuals classified according to the CVD risk from high risk to desirable. The percentage of samples at the various levels of risk according to each test method is shown in Figure 2.

Using the ATP III recommended high CVD risk cutoff of greater than 6.0 for the LDL-C/HDL-C ratio, only 0.4% (5 samples) was classified high risk Type A, 14% were classified Type B, 11% were classified borderline high or Type B and 6% were classified Type C or moderate high. The lowest number of borderline high or Type B was 21 (95.4%) out 22 based on the NMR LDL particle number. Of the 21 high risk individuals, 9 were classified high risk by the NMR LDL particle number. Of the 21 high risk individuals, 9 were classified high risk by the NMR LDL particle number. Of the 21 high risk individuals, 9 were classified high risk by the NMR LDL particle number. Of the 21 high risk individuals, 9 were classified high risk by the NMR LDL particle number. Of the 21 high risk individuals, 9 were classified high risk by the NMR LDL particle number. Of the 21 high risk individuals, 9 were classified high risk by the NMR LDL particle number. Of the 21 high risk individuals, 9 were classified high risk by the NMR LDL particle number. Of the 21 high risk individuals, 9 were classified high risk by the NMR LDL particle number.

The results of this study indicate that the number of individuals classified as moderate or high risk of CAD varies with the test method. The methods for assessing CAD risk have continued to be the subject of much debate. In November 2013, the ACC/AHA Task Force released new guidelines and a new CVD risk calculator based on data from randomized control trials. The risk calculator weighs heavily on non-risk lipid factors reducing the role of LDL-C and other lipid measurements as risk factors.

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According to the ASCVD risk calculator, 7 (31.8%) of the 22 individuals were at high risk of CVD. Five of the seven samples were classified high risk based on non-lipid risk factors such as hypertension, diabetes and advanced age and only 2 were classified as the results of dyslipidemia. Based on the Lipoprint LDL subfractions, 15 (68.2%) of the individuals were classified intermediate or high risk. Interestingly, each of the 9 samples classified high risk by Lipoprint was also classified high risk by one or more other method. The borderline high and high risk individuals varied between 54% and 59% according to the other test methods. The findings of this study suggest that the ASCVD risk calculator appears to underestimate the risk associated with dyslipidemias when compared to other methods while the Lipoprint LDL subfractions test appears to capture all the high risk individuals classified as high risk by all the other methods. Considering the fact that CVD is a life long progressive disease, early recognition is very important in primary prevention and treatment. Use of the Lipoprint LDL test to measurement of the triglyceride enriched VLDL remnants, IDL and small dense LDL subfractions could provide early identification of individuals at risk for CVD.

**Conclusion**

Results from this study suggest the following points:

- The traditional lipid profile including total cholesterol, triglycerides, LDL-C and HDL-C do not always appear to discriminate between individuals at increased risk of CVD from low risk individuals especially among borderline high individuals.
- An individuals risk classification may vary with the test method used. Some methods classify most at risk samples while others classify very few at risk samples.
- Measurement of small dense LDL, VLDL remnants and IDL using the Lipoprint LDL subfraction test identified all the individual classified as high CVD risk from all the other test methods combined.
- Large buoyant LDL cholesterol as measured by the Lipoprint LDL Subfractions Test was not associated with increased CVD risk.
- The NMR LDL-P method classified 72.7% of the test samples as high risk which accounted for approximately 100% more than the other test methods.
- In the studied population, non traditional lipid testing methods such as total cholesterol to HDL-C ratio and triglycerides appeared to be better CVD risk indications than the traditional lipid profile based on LDL-C.
- The new ACC/AHA guideline’s recommendations are very useful for preventing CVD events in individuals with existing CVD and diabetes; however, they appear to be less helpful in identifying CVD risk in younger and older individuals in primary prevention.
- The Lipoprint LDL subfractions test identified all the individuals classified as high risk by the other test methods other than NMR LDL-P that identified twice as many high risk individuals than all the other test method.
- This study suggests that the Lipoprint LDL test appears to identify individuals at risk for CVD due to dyslipidemia in both the young and the old and could be helpful in primary prevention in individuals not recognized by the new ASCVD risk calculator.

![Figure 1: Lipoprint LDL Profile](image1)

![Figure 2: CVD Risk Assessment Methods Comparison](image2)

**Table 1: CVD Risk Data**

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