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Dyslipidemia: The Role of Non-HDL Cholesterol, Apolipoprotein B and Small, Dense LDL

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ABSTRACT

Elevated low-density lipoprotein cholesterol (LDL-C) has traditionally been considered as an independent risk factor for coronary artery disease (CAD). A level of LDL-C< 70 mg/dl is recommended for very high risk individuals. However, it has recently been suggested that the threshold for atherosclerosis may be much lower and it is widely accepted that even with the intense use of statins, not all cardiovascular adverse events are prevented. Consequently, new indexes have emerged that could outperform LDL-C especially in the highest risk populations, such as patients with diabetes type II or the metabolic syndrome. Non- HDL cholesterol is defined as all of the cholesterol that is not HDL (total cholesterol- HDL cholesterol). It has been shown that for each LDL-C category, according to NCEP- Adult Treatment Panel III, an increase in non-HDL cholesterol increased the risk for cardiovascular disease. It seems that the combination of a high concentration of triglyceride- rich particles and LDL-C carries a particularly high risk and increasing VLDL and IDL concentrations add to the risk at any LDL concentration. Total apo-B level reflects the total number of apo- B lipoproteins and measures the total atherogenic particle number. It seems that apo-B levels are much more closely related to the risk of vascular events than LDL-C or non-HDL cholesterol as presented in many large prospective trials. There are at least seven distinct subclasses of LDL of different particle sizes and several recent studies have suggested that LDL subfraction distribution, especially the presence of increased levels of small, dense LDL particles, aid in the prediction of cardiac heart disease risk. Further studies will clarify the clinical circumstances that justify lipoprotein analysis and how to best use the information taken from new indices such as non-HDL, apolipoprotein B or small dense LDL particles, in the management of our patients.

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Cardiovascular disease is the leading cause of death in the developed countries and in a few decades it will become the leading cause of death in the developing world as well[1]. Therefore, the early identification of individuals at increased risk is of pivotal importance in order to modify the factors contributing to this high risk profile.

Elevated low-density lipoprotein (LDL) cholesterol has traditionally been considered as an independent risk factor for coronary artery disease (CAD). A number of trials have suggested that lowering LDL-cholesterol leads to a decrease in the incidence of CAD[2-5]. Moreover recent randomized statin trials have found progressively lower risk with progressively lower LDL-C levels[6,7]. The National Cholesterol Education

Program (NCEP) Adult Treatment Panel (ATP) endorses LDL-C as the basis for risk stratification and treatment goal[8]. A level of LDL-C< 70 mg/dl is recommended for very high risk individuals. However, it has recently been suggested that the threshold for atherosclerosis may be much lower[3] and it is widely accepted that even with the intense use of statins in order to achieve the aforementioned goals, not all cardiovascular adverse events are prevented[9]. Consequently, researchers are trying to identify new indexes that would outperform LDL-C especially in the highest risk populations such as patients with diabetes type II or the metabolic syndrome. Therefore, the role of non-HDL cholesterol, apolipoprotein B levels and small dense LDL particles as independent predictors of cardiovascular disease is currently under evaluation.

NON- HDL CHOLESTEROL

Non-HDL cholesterol is defined as all of the cholesterol that is not HDL (total cholesterol- HDL cholesterol) and comprises the cholesterol concentration of all the apoB- lipoproteins, i.e. VLDL, LDL, IDL and lipoprotein(a) . If the triglyceride level is more than 200 mg/dl, the increase of non-HDL cholesterol reflects the increase of triglyceride rich lipoproteins i.e. VLDL. Recent data suggest that non-HDL-C is a good predictor of initial CAD and independent of the levels of LDL[11]. Conducting analysis of the Framingham database, Liu et al. demonstrated that the risk for CAD associated with high non-HDL cholesterol was independent of LDL- C concentration. Moreover, for each LDL-C category, according to NCEP-ATP III, an increase in non-HDL cholesterol increased the risk. It seems that the combination of a high concentration of triglyceride- rich particles and LDL-C carries a particularly high risk and increasing VLDL and IDL concentrations add to the risk at any LDL concentration. Moreover, non-HDL-C has been associated with recurrent episodes of angina pectoris and nonfatal myocardial infarction in patients with multivessel CAD[12]. Data from the Lipid Research Clinic Program cohort study[13] were used to compare the predictive value of non-HDL-C as a risk factor for cardiovascular mortality with LDL-C. The follow-up period was 19 years. In men as well as in women, an increase in non-HDL-C level was associated with an increase in cardiovascular mortality and the relative risk was 2.14 in men with non-HDL-C >220 mg/dl compared to those with non-HDL-C < 160 mg/dl. In patients with hypertriglyceridemia or the metabolic syndrome, the NCEP- ATP III introduced non-HDL-C as a treatment target and many authors have supported the suggestion to estimate non-HDL C when assessing the risk in patients with low to normal LDL- C and treating targets are calculated by adding 30 mg/dl to the standard NCEP-ATP III target LDL-C.

APOLIPOPROTEIN B

Each one of the atherogenic lipoproteins, i.e. each chylomicron, VLDL, IDL, LDL, and lipoprotein(a) contain only 1 molecule of apo-B. Therefore, the total apo-B level reflects the total number of apo- B lipoproteins and measures the total atherogenic particle number. Thus, in a patient with normal LDL-C, high apo-B levels may reflect higher number of small, dense, highly atherogenic LDL particles. Apo-B binds the atherogenic lipoproteins to proteoglycans on the arterial wall, thus facilitating the integration of cholesterol in the macrophages of the subendothelial space which transform into foam cells. Moreover, the oxidation of apo-B creates proinflammatory products that propagate atherosclerosis in the arterial wall[14]. Apo-B is more closely related to inflammatory markers than total cholesterol, LDL-C or non-HDL-C[15]. This relation was superior to many other risk factors including body mass index, abdominal obesity, systolic blood pressure, fasting glucose, etc. Finally, the value of apo-B levels in the prediction of metabolic syndrome and diabetes, particularly in women has been shown[16]. It seems that apo-B levels are much more closely related to the risk of vascular events than LDL-C or non-HDL-C as presented in many large prospective trials such as the AMORIS[17] study, the Health Professionals Follow-up Study[18] and the Quebec Cardiovascular Study[19]. In the latter study, non-HDL-C was strongly correlated with apo-B across all cardiac heart disease categories (r=0.9) and this correlation was much stronger than the correlation between LDL-C and apo-B, which became weaker with increasing triglyceride levels. Moreover, this study showed that in patients with CAD, both non-HDL cholesterol and apo-B levels were significantly elevated compared to LDL- C, so greater reduction in non- HDL cholesterol and apo-B than LDL-C would be required for optimal risk management. Finally, apo-B appears to be a better predictor of subsequent CAD events in patients on treatment with statins[20]. However, despite the clinical importance of apo-B levels, the cost and difficulties in the measurement due to lack of standardization across centers precludes its widespread clinical use.

SMALL DENSE LOW-DENSITY LIPOPROTEIN

There are at least seven distinct subclasses of LDL of different particle sizes. Several recent studies have suggested that LDL subfraction distribution aids in the prediction of cardiac heart disease risk. The Quebec Cardiovascular Study[19] confirmed a strong association in men of the cholesterol content in small dense LDL (LDLc <255E) with the risk for ischemic heart disease compared with the relationship of large LDL (>260 E) to the risk that was weak. This strong association was independent of factors such as HDL-C, triglyceride and apolipoprotein B. In an analysis of subjects with the metabolic syndrome in the Framingham Heart Study[21], small LDL particle level was increasing with an increasing number of metabolic syndrome traits and those with the syndrome had higher risk for cardiac heart disease. Other studies have confirmed that subjects with increased small, dense LDL levels exhibit also increased VLDL, small, dense HDL and low total HDL levels[22]. It seems that central obesity leads to an increase content of fat in the liver with subsequent increased production and secretion of VLDL. Insulin resistance disturbs the correct regulation of VLDL production and low adiponectin is associated with low VLDL clearance rate. Increased VLDL levels is the key feature of a dyslipidemic syndrome which initiates a sequence of events that generates the atherogenic small, dense LDL and HDL particles and it is common in diabetes, in the metabolic syndrome, in familial combined hyperlipidaemia, in preeclampsia, etc[22,23]. However small, dense LDL levels failed to predict the onset of frank diabetes in prediabetic subjects whereas VLDL and small HDL concentration appeared to be related to future onset of diabetes[24].

The role of small, dense LDL cholesterol in the pathogenesis and progression of the atheromatous plaque has recently been elucidated. Small, dense LDL is more easily oxidized and is subject to a higher degree of retention in the arterial wall. Small, dense LDL also exhibits reduced binding capacity to the LDL-receptor, thus is staying longer in the circulation and is subject to more structural changes which can increase its atherogenic potential. Small, dense LDL promotes endothelial dysfunction, inducing greater production of plasminogen activator inhibitor (PAI)-I and thromboxane A_2[25]. Interventions that would modify small, dense LDL level include administration of statins that reduce all LDL subfractions, administration of fibrates in which case the benefits are greater in individuals with a predominance of small, dense LDL particles and apparently peroxisome- activated receptor γ agonists seem to be able to alter particle size in diabetes, metabolic syndrome, and in hypertension without a change in plasma VLDL or triglyceride concentration[26].

CONCLUSION

Increasing number of studies are supporting the incremental value of measuring non-LDL and especially apolipoprotein-B. Patients already on statins with high apo-B plasma level may still have too many small, dense LDL particles which are highly atherogenic and may warrant more aggressive approach and management maybe in the form of combination of lipid-lowering drugs. Current guidelines clearly set LDL-C as the primary target of lipid lowering therapy and introduce non-HDL as a secondary target of therapy in patients with elevated triglycerides level (≥200 mg/dl)[8]. As for the therapeutic strategies, statins remain the mainstay of treatment for increased LDL as well as non-HDL cholesterol even as monotherapy. When LDL cholesterol is extremely high, a combination of drug therapy is advised, e.g. statins and bile acid sequestrant in order to reach the therapeutic goal.

Ezetimibe has complementary action to the statins adding an extra 20% LDL reduction and its clinical significance was studied in the ENHANCE trial[27] that was published earlier this year. The results were disappointing and raised much speculation since the study failed to show any benefit in the intima media thickness in the carotid arteries from the treatment with the combination of simvastatin and ezetimibe compared to simvastatin alone. Fibrates are considered for monotherapy only when triglycerides are over 500 mg/dl due to high risk of acute pancreatitis. However, when triglycerides fall below 500 mg/dl, LDL becomes again the primary target of therapy and statins are usually combined with a fibrate or nicotinic acid. The latter two drugs also increase HDL. However, ATP III does not specify a certain goal for HDL in patients with decreased levels as in the metabolic syndrome and outline the importance of LDL lowering as a primary target. Adding a drug such as a fibrate in a patient with low HDL after reaching LDL target may be considered in high risk populations. Torcertapib, a cholesteryl ester transfer protein (CETP) inhibitor was a promising drug that could substantially increase HDL cholesterol. However, a phase III trial, the ILLUMINATE trial,[28] was terminated early because an interim analysis showed an increased rate of mortality in patients receiving the combination of atorvastatin and torcetrapib compared to those receiving atorvastatin alone.

Finally, it is very important to note that a majority of high risk patients even on a statin have very high levels of LDL cholesterol according to the ASPIRE[29] and EUROASPIRE[30] registries. Therefore, all possible interventions should be implemented in patients according to the existing guidelines in order to reach the therapeutic targets and consequently reduce mortality and risk for cardiovascular events. Further large scale prospective clinical trials will clarify the clinical circumstances that justify further lipoprotein analysis and how to best use the information taken from new indices such as non-HDL, apolipoprotein B or small dense LDL particles, in the management of our patients.

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