MEASUREMENT OF SMALL LOW DENSITY LIPOPROTEIN (LDL) PARTICLES
MED207.008
POSTED DATE: 8/22/2003
EFFECTIVE DATE: 12/1/2003

COVERAGE:

Measurement of small low-density lipoprotein (LDL) particles is considered experimental or investigational.

DESCRIPTION:

A high serum cholesterol level is recognized as a major risk factor for coronary heart disease (CHD). Much of serum cholesterol is transported in low-density lipoproteins (LDL) and LDLs are considered the most atherogenic component of serum cholesterol. In fact, the National Cholesterol Education Program has designated LDL cholesterol as the primary target of cholesterol-lowering therapy. Statin therapy (i.e., HMG CoA reductase inhibitors) mainly lower LDL; clinical trials have shown that the use of these drugs has resulted in a significant reduction in new coronary events.

However, LDL particles are not uniform in size or density, and two subclass patterns, A and B, have been described. In subclass pattern A, the diameter of the LDL particles are larger than 25 nm, while in subclass pattern B the particle diameter is less than 25 nm. Subclass pattern B is frequently associated with a more atherogenic lipoprotein profile (referred to as ALP) than subclass pattern A, consisting of higher levels of triglyceride, apoprotein B (which reflect the number of LDL particles, as opposed to their content), intermediate density lipoprotein (IDL), very low density lipoprotein (VLDL) and lower levels of high density lipoprotein (HDL). An increased prevalence of small dense LDL particles has been noted in patients with CAD. In addition, LDL subclass pattern B is a commonly inherited lipoprotein disorder that has been linked to a position on the short arm of chromosome 19 and several other loci.

Therefore, LDL particle density or diameter has been proposed as a technique to further risk stratify patients with elevated LDL levels, or to risk stratify patients with normal LDL levels but with other high risk factors for CAD, or to predict response to therapy. LDL particle diameter can be measured using ultracentrifugation while density can be measured by gradient gel electrophoresis (GGE). GGE is the most commonly used laboratory technique.

RATIONALE:

Small dense lipoprotein particles have been extensively investigated in 3 different clinical contexts.

1. As a separate independent risk factor for CAD
Epidemiologic studies have suggested that small-diameter LDL particles...
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are associated with an increased risk of CAD. For example, a 1996 prospective study reported that small LDL particles may play some role in atherogenesis. Another 1996 study investigated whether LDL particle size was an independent predictor of CAD risk, particularly in comparison to triglyceride levels. This prospective study of almost 15,000 men concluded that while LDL particle diameter was associated with risk of myocardial infarction, this association was not present after adjustment for triglyceride level. Only triglyceride level was significant independently. Another 1997 prospective study reported somewhat conflicting results; in this study of 2,100 men, levels of small LDL particles appeared to be a “partially” independent predictor of ischemic heart disease. Therefore, the clinical relevance of small, dense LDL particles is unclear, since they may not provide additional risk stratification beyond that available from the more readily available measurement of triglycerides. In addition, there are no published data regarding how treatment decisions may be guided as the result of measurement of small LDL particles.

2. As a risk factor in normocholesterolemic patients with known CAD

Approximately 80% of patients with CAD, as evidenced by a history of acute myocardial infarction, angina, or coronary artery stenosis as seen on angiogram, will have normal serum levels of cholesterol. Subclass pattern B may have a higher prevalence in this normocholesterolemic population, and levels of LDL and HDL may be related to disease progression. While these investigations may contribute to understanding the pathogenesis of CAD in normocholesterolemic patients, it is not known how measurements of small LDL particles may guide treatment decisions.

3. As a predictor of response to treatment

Patients with subclass pattern B have been reported to respond more favorably to diet therapy compared to those with subclass pattern A. Subclass pattern B has also been shown to respond more favorably to the drug gemfibrozil and niacin, with a shift from small, dense LDL particles to larger LDL particles. While statin drugs lower the overall concentration of LDL cholesterol, there is no shift to the larger LDL particles. The Stanford Coronary Risk Intervention Program (SCRIP) trial studied the relationship between small, dense LDL and the benefit of diet, counseling, and drug therapy in patients with CAD, as identified by initial coronary angiogram. The principal outcome was changes in the results of coronary angiogram after 4 years. Patients with subclass pattern B showed a significantly greater reduction in CAD progression compared to those with subclass pattern A. While subclass pattern B may predict response to therapy; it is unclear how subclass pattern B should influence the choice of therapy, particularly in relation to other associated abnormalities, i.e.,
triglyceride levels.

In summary, while the recognition of different subclasses of LDL particles has provided a powerful research tool into the hereditary patterns of CAD and its pathogenesis, the direct clinical application of measuring small, dense lipoprotein particles is still unclear. Specifically, there are inadequate published data to determine how such measurements should guide treatment decisions and whether these treatment decisions result in beneficial patient outcomes. In addition, it is unclear whether measurements of small dense lipoproteins provide additional information regarding risk stratification and treatment selection beyond that provided by the more readily available measurements of other markers of subclass pattern B, i.e., levels of triglyceride, HDL, or IDL.

An additional search and review of literature was completed through the MEDLINE database for the period of January 2000 - January 2003. No additional information was reviewed that would alter the above conclusions.

PRICING:

None

REFERENCES:

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