UC San Diego Health

# A Novel Blood Test Measuring Oxidized Fats Is A Powerful Heart Disease Indicator

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San Diego, CA – Even though heart disease is the nation's number one killer, little is known about the disease's early stages, as fats (lipids) accumulate within artery walls, creating the atherosclerosis that leads to heart attacks. By measuring specific oxidized phospholipid molecules in the blood, a University of California, San Diego (UCSD) School of Medicine-led team found that the levels of this toxic molecule circulating in the bloodstream strongly reflect how much blockage is present in the coronary arteries. This measurement could help doctors better determine the risk of a heart attack, and provide a new target for drug development.

The study, published in the July 7, 2005 *New England Journal of Medicine*, and led by Sotirios "Sam" Tsimikas, M.D., UCSD Associate Professor of Cardiology and Director of Vascular Medicine, presents two key findings based on a new test developed by Tsimikas, Joseph Witztum, M.D., UCSD Professor of Medicine, and colleagues:

- → A new test to detect oxidized phospholipids in the bloodstream strongly predicts the presence of coronary blockages, especially in patients younger than 60 years old who also have elevated cholesterol levels.

- → These oxidized phospholipid particles are strongly attached to another cholesterol-containing lipoprotein that circulates in the bloodstream called Lp(a), which might explain why Lp(a) may be atherogenic.

Lp(a), discovered in the 1960s, has received little attention by researchers for the last decade due to the lack of understanding of its role in atherosclerosis. This study suggests that Lp(a), which has a strong affinity for binding to the blood vessel wall, may play a key role in developing atherosclerosis as a "partner in crime" with oxidized phospholipids. Both are known to be highly pro-inflammatory.

The risk attributable to Lp(a) may in fact be due to its ability to bind and travel with oxidized phospholipids, attaching these toxic particles to the vessel walls, where they then may induce inflammation that can lead to blocked arteries.

"We've known about other lipid risk factors for years, such as elevated Low Density Liposprotein (LDL) cholesterol (bad), low levels of High Density Lipoprotein (HDL) cholesterol (good), and elevated triglycerides," said Tsimikas. "Lp(a) appears to be another risk predictor, particularly in patients with abnormal cholesterol levels, but it has not been determined how it actually causes arterial blockages.

"This study provides a potential explanation, and shows that high levels of oxidized phospholipids and Lp(a) are tightly associated with coronary heart disease, indicating that they could be useful tests to determine risk in patients," he said. "It also demonstrates that these molecules could be promising targets for pharmaceutical research, particularly in developing new drugs to reduce their levels in the bloodstream and in the vessel wall."

The team analyzed blood samples from 500 patients being treated for heart problems at the Mayo Clinic in Rochester, MN, including the clinical and laboratory risk factors associated with atherosclerosis and heart disease in patients who were referred for coronary angiography, a procedure to determine blockage in the coronary arteries. They found that levels of oxidized phospholipids could predict the presence of coronary blockages even after taking into account all other known risk factors such as abnormal cholesterol levels, high blood pressure, smoking and gender.

Interestingly, said Tsimikas, the risk attributable to oxidized phospholipids was nearly identical to the risk attributable to Lp(a) in the overall group, but in patients under 60 years old, the oxidized phospholipid measure was a strong indicator, independent of Lp(a). This suggests that oxidized phospholipids may be more powerful determinants of risk for coronary artery disease in patients younger than 60 years old compared to those older than 60 years old.

"These results suggest that Lp(a) and oxidized phospholipid levels are very tightly linked and each helps the other contribute toward atherosclerosis when found at high levels in the blood," Tsimikas said. "These two molecules may be working differently in younger patients, so that oxidized phospholipids may generate additional risk above and beyond Lp(a). As this is the first study to show this, further confirmation will be required in other studies."

He noted that while elevated LDL cholesterol levels alone were very strong predictors of coronary artery disease, the combination of oxidized phospholipids with elevated cholesterol levels was the highest predictor for determining the presence of coronary blockages, showing a 16-fold higher risk for coronary blockages in those with the highest levels of both compared to the lowest levels of both. This suggests that these biomarkers may provide improved diagnostic accuracy in patients, above and beyond knowing the cholesterol levels.

Levels of Lp(a) in the blood are genetically determined, said Tsimikas, which means that patients with elevated levels have them starting at birth. This may explain why these biomarkers are more predictive in younger patients. Elevated Lp(a) levels are found in approximately 25% of the population. This also implies that in patients found to have high Lp(a) levels, one of the parents had the gene for developing high Lp(a) levels, and approximately half of the siblings will also have it. Thus, it is important to review the family history to determine additional family members that may be at risk.

Levels can also increase when an acute stress occurs, such as a heart attack, but generally return to their baseline over months. Clinical tests are available that can measure Lp(a) levels in a clinic, providing physicians with a tool to determine which patients may be at the highest risk of heart disease. The test to measure oxidized phospholipid levels is not yet available for clinical use, and more studies such as this one will be required to prove its clinical utility and whether it provides independent information in addition to knowing Lp(a) levels.

"The finding that Lp(a) binds to oxidized phospholipids also allows us to hypothesize that it may have a potential beneficial function in clearing these toxic particles from the circulating blood. However, as too much of a good thing can be detrimental, it is possible that low levels of Lp(a) may be beneficial, but high levels are associated with higher rates of heart disease, suggesting that testing for Lp(a) levels could help determine a patient's risk for the presence of current or future heart disease," said Tsimikas.

"For this reason I think it is important for physicians to consider measuring Lp(a) in patients with coronary risk factors, particularly a strong family history of heart disease, or those patients that suffer from heart problems at a relatively young age," Tsimikas suggested.

Tsimikas and his team are now working on more prospective studies, in which they can follow the development of blood levels of Lp(a), oxidized phospholipids and other proteins, and determine if high levels of these molecules and the formation of atherosclerotic plaque can be prevented. In addition, the researchers believe that Lp(a) could be a promising drug target, as reducing its levels could reduce the binding to oxidized molecules that lead to clogged arteries. Currently the only drug that can consistently reduce Lp(a) levels is niacin, but further efforts are required to find more effective drugs.

Tsimikas' colleagues in the study included Joseph Witztum and Elizabeth Miller of the UCSD School of Medicine; Emmanouil Brilakis, Joseph McConnell and Ryan Lennon of the Mayo Clinic; Kenneth Kornman of Interleukin Genetics, Waltham, MA; and Peter Berger of Duke University.

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