Sphingolipid fingerprint predicts heart disease severity in African American lupus patients

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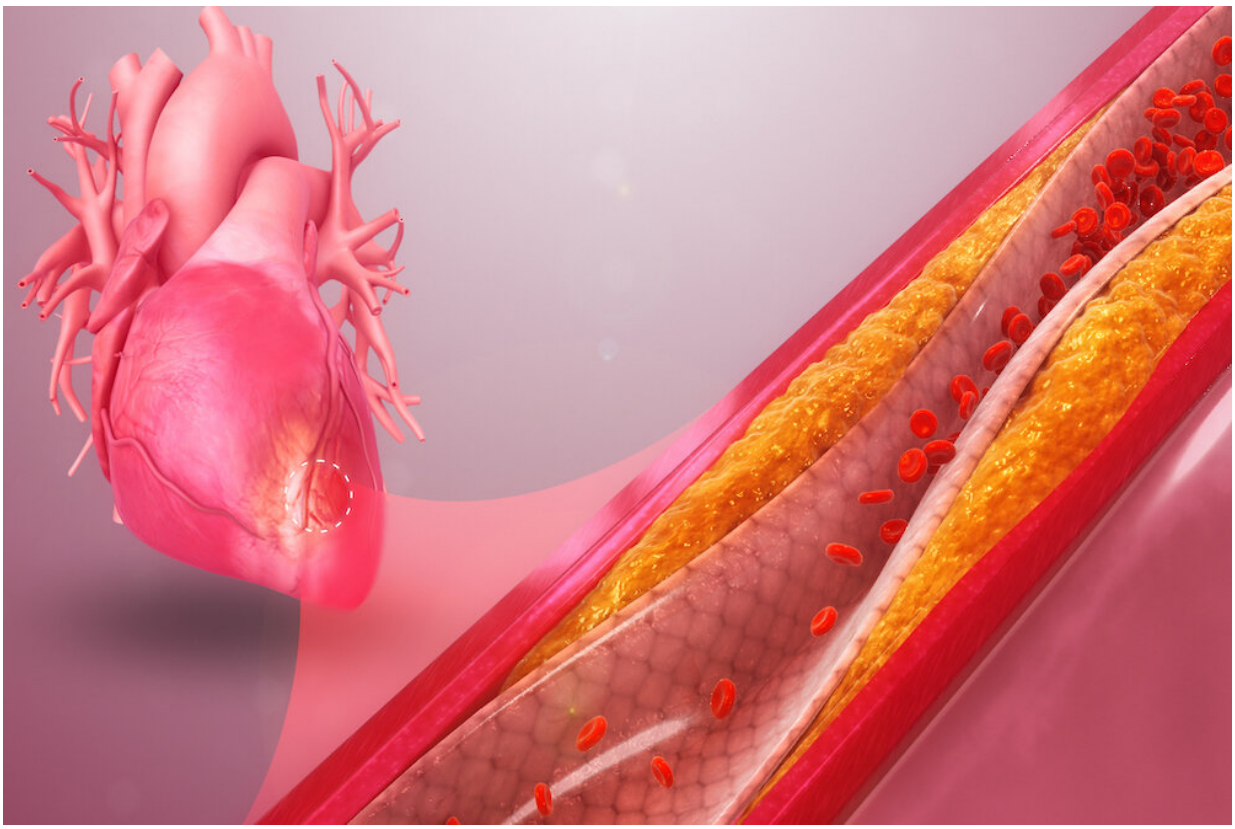

3D still showing myocardial ischemia. Credit: Licensed from http://www.scientificanimations.com, via the Creative Commons 4.0 license, available at https://creativecommons.org/licenses/by-sa/4.0/deed.en

A team of MUSC researchers report in *Frontiers in Immunology* that they have identified a type of fat known as a sphingolipid that could predict the severity of heart disease in African American patients with lupus.

The team was led by Samar M. Hammad, Ph.D., associate professor in the MUSC College of Medicine, and the study was funded in part by a pilot project grant from the South Carolina Clinical & Translational Research Institute.

"The most exciting finding of this study is that we may be able to find another way to better diagnose and eventually treat the African American lupus patients who are at increased risk of developing heart disease," said Hammad.

Systemic lupus erythematosus (SLE), or lupus, is a chronic autoimmune disease that can affect many different organs in the body. Our immune system typically acts like our personal bodyguard. When it senses danger from a virus or infection, it attacks and eliminates the threat. In patients with SLE, the "bodyguard" attacks and damages the person's own cells, mistaking them as foreign invaders. As a result, patients with SLE can develop complications, such as cardiovascular disease (CVD).

Cholesterol, a type of fat circulating in our blood, is carried on lipid particles called high-density lipoproteins (HDL, the good cholesterol carrier) and low-density lipoprotein (LDL, the bad cholesterol carrier) and typically used to screen for CVD. High levels of LDL cholesterol are commonly used to predict a patient's risk for developing heart disease because this fat accumulates in the walls of blood vessels.

Despite being at an increased risk of CVD, healthy African Americans have a lipid profile with higher HDL (good) cholesterol and lower triglyceride levels compared with healthy persons of European ancestry. Therefore, the efficacy of the standard screening method for CVD has

been called into question for African American patients. Further, approximately 90% of lupus patients are females, and African American women are three times more likely than white women to develop severe symptoms associated with SLE. Thus, the standard screening panels, developed with the white patient in mind, lack efficacy for the African American patient. With the standard method of screening for CVD potentially being unreliable for African American SLE patients, additional biomarkers are needed to improve health outcomes in this group.

Sphingolipids are molecules carried in the blood on lipoproteins. They are important structural components of cells, can act as key signaling molecules, and when disrupted, are associated with several diseases. Recently, serum sphingolipids have been shown to be potential biomarkers for clinical lupus complications.

Notably, the Hammad lab previously found that the sphingolipid profile of healthy African Americans differs from that of healthy whites. They also observed differences in the sphingolipid profiles of African American lupus patients with or without heart disease.

"Treatments for SLE and heart disease are often given as a one-size-fits-all, and they can have major side effects for the patient," said Hammad.

The purpose of this study was to determine whether sphingolipids are predictive biomarkers for preclinical CVD and CVD severity in African American patients with SLE. At the study start (visit 1) and after one year (visit 2), the researchers measured levels of five different sphingolipid classes, with several sphingolipid species in each class, in plasma samples of 51 patients with SLE but without a history of clinical heart disease.

Hammad and her lab established a methodology for profiling

sphingolipids in human plasma in 2010 that is now widely used in sphingolipid studies. Using this method, Hammad and her team found that a particular class of sphingolipid in the plasma samples, called lactosylceramide (Lac-Cer), was positively correlated with the change in plaque area over one year. Plaques are clumps of cholesterol found at injury sites of walls of major arteries. Thus, higher levels of Lac-Cer are associated with increased disease activity in African American patients with SLE.

"This finding showed us that the Lac-Cer levels in the circulation could have predictive value for a patient," explained Hammad. "We could use this as a readout for how a patient is progressing while on medication and get a good indication of his or her heart disease."

High LDL cholesterol content in the serum is typically used to determine the risk of developing heart disease. The study found no correlation between LDL concentrations and the concentrations of the measured Lac-Cer species, indicating that the traditional biomarker for heart disease was ineffective in predicting disease severity in the African American lupus population.

Ultimately, Hammad believes that studies like these emphasize the need for teamwork between basic scientists and clinicians.

"I'm a basic scientist who has almost 20 years of experience in investigating the role of sphingolipids in health and disease," said Hammad. "This study was possible, thanks to the organized and well thought out collection and banking of patient samples from the clinical side, led by Dr. Jim Oates, division director of Rheumatology and Immunology."

Future objectives of the team will include determining whether their findings can be applied to the general population.

"Using sphingolipids as a tool to complement other diagnostic modalities will be important because SLE is often hard to diagnose," said Hammad. "I think sphingolipids can play a major role in the diagnosis, prognosis and treatment of lupus."

More information: Samar M. Hammad et al, Plasma Sphingolipid Profile Associated With Subclinical Atherosclerosis and Clinical Disease Markers of Systemic Lupus Erythematosus: Potential Predictive Value, *Frontiers in Immunology* (2021). DOI: 10.3389/fimmu.2021.694318

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