Researchers identify lipid profile characteristic of newly diagnosed type 1 diabetes

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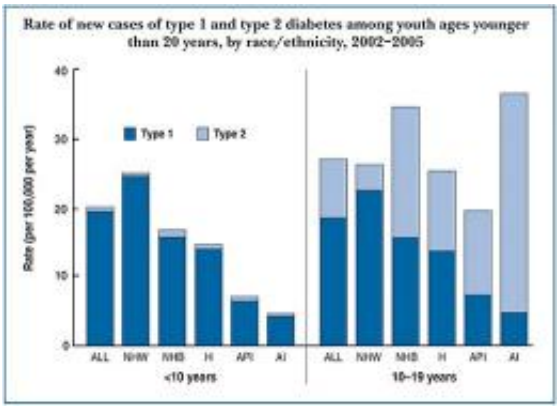

Source: SEARCH for Diabetes in Youth Study NHW=non-Hispanic whites; NHB=non-Hispanic blacks; H=Hispanics/Latinos; API=Asian/Pacific Islander Americans; AI=American Indians

(PhysOrg.com) -- A journal article showcasing results of lipidomics analyses for identifying novel biomarkers of diabetes conducted at Pacific Northwest National Laboratory was selected as "Editor's Choice" by two clinical chemistry scientific journals. The paper, "Perturbations in the lipid profile of individuals with newly diagnosed type 1 diabetes mellitus: lipidomics analysis of a Diabetes Antibody Standardization Program sample subset," published in *Clinical Biochemistry*, described lipidomics analyses of blood samples from patients recently diagnosed with type 1 diabetes mellitus (T1DM).

The Editors-in-Chief of *Clinical Biochemistry* and *Clinica Chimica Acta* selected the paper for the distinction and included it in a booklet distributed at international meetings sponsored by the International Federation of Clinical Chemistry.

T1DM affects more than 1 million individuals in the United States alone. Currently, the best approach for predicting those at risk for developing T1DM before symptoms appear is by measuring autoantibodies to islet cell antigens in the pancreas.

Lipids 101

Lipids are one of the four major molecular components of biological organisms, along with proteins, sugars, and nucleic acids. They store energy, make up the structures of cells, and participate in cell signaling. The "lipidome" refers to all lipids in cells and "lipidomics" to the measurement thereof.

Autoantibodies cause many autoimmune diseases. Multiple autoantibody positives and their persistence are unequivocally related to the risk of progression to T1DM. However, autoantibodies are difficult to measure with consistent sensitivity and specificity, and assay performance varies considerably among laboratories. Sound methods are needed to identify new biomarkers that predict T1DM development and can also be transferred to other laboratories.

To improve and standardize measurement of autoantibodies associated with T1DM and identify novel protein biomarkers, the Centers for Disease Control and Prevention (CDC) and the Immunology of Diabetes Society created the Diabetes Antibody Standardization Program (DASP). Scientists at PNNL and the CDC previously conducted a global proteomics analysis of plasma and serum samples from the DASP and identified five candidates in a sample subset (Metz et al. 2008).

The role of ZAG: Scientists found that one protein in particular, zinc alpha-2-glycoprotein (ZAG), was strongly upregulated, or increased, in individuals with T1DM. ZAG, a member of the immunoglobulin superfamily, is responsible for lipid mobilization. This means that increased levels of ZAG in patients may indicate a system-wide mobilization of lipids for energy production, particularly because these individuals lack endogenous insulin and cannot rely on blood glucose (sugar) for their energy needs. The scientists hypothesized that perturbations, or changes, may be present in the blood lipidome of individuals with newly diagnosed T1DM.

To test their hypothesis, they performed lipidomics analyses on the same DASP samples to identify perturbations in the lipids of individuals with recently diagnosed T1DM and to potentially identify a lipid profile that could predict or diagnose the disease.

"When discussing lipids in the context of personal health, most people think of total cholesterol, HDL, LDL, and triglycerides, which are the lipids typically measured in a blood lipid panel at clinics and hospitals," said PNNL chemist Dr. Thomas Metz. "They don't realize that there is a broad diversity of lipids in blood and tissues—thousands of individual lipid molecular species comprising about a dozen or so major classes.

"For example, HDL and LDL themselves are comprised of hundreds of molecular species of cholesterol esters and triglycerides. So, while the typical clinic blood lipid panel may not indicate differences in total cholesterol, HDL, LDL, and triglycerides, there may be dramatic changes at the level of lipid molecular species. These are the changes that only mass spectrometry can identify with sufficient sensitivity and throughput."

The scientists used capillary liquid chromatography (LC) coupled with Fourier transform ion cyclotron resonance (FTICR) mass spectrometry

(MS) and the accurate mass and time (AMT) tag approach developed at PNNL to identify and quantify lipids present in healthy and diabetic individuals. The AMT tag approach relies on initial, low-throughput shotgun LC-MS/MS analyses to populate a database of identified molecules followed by higher throughput and more quantitative LC-MS analyses.

They identified more than 559 lipids that were significantly different (q

"The patients in our study had well-controlled blood glucose levels, so their blood lipid panels showed no differences in total cholesterol, HDL, LDL, and triglycerides compared to the controls," Metz said. "In that respect, it is very exciting that we identified so many lipid molecular species that showed statistically significant differences between the patients and controls. It really highlights an area worth further study in the context of T1DM."

More information: Sorensen CM, J Ding, Q Zhang, T Alquier, R Zhao, PW Mueller, RD Smith, and TO Metz. 2010. "Perturbations in the lipid profile of individuals with newly diagnosed type 1 diabetes mellitus: lipidomics analysis of a Diabetes Antibody Standardization Program sample subset." *Clinical Biochemistry* 43(12):948-956.

Metz TO, W-J Qian, JM Jacobs, MA Gritsenko, RJ Moore, AD Polpitiya, ME Monroe, DG Camp II, PW Mueller, and RD Smith. 2008. "Application of Proteomics in the Discovery of Candidate Protein Biomarkers in a Diabetes Autoantibody Standardization Program Sample Subset." *Journal of Proteome Research* 7(2):698-707.

Provided by Pacific Northwest National Laboratory