Key Summary of Conference Abstract

A Proteomic Predictor of Lipoprotein Function and Coronary Artery Disease: From Conception to Launch

Background

- High-density lipoprotein (HDL) is a well-established biomarker of cardiovascular health, but risk assessments traditionally rely on measuring HDL levels as opposed to function.
- Cholesterol efflux capacity (CEC) is a measure of HDL function and has been shown to be predictive of cardiovascular events.[1,2]
- However, measurement of CEC has depended on slow, low-throughput, cell-based assays, which prevent broad use of the biomarker to assess cardiovascular disease risk.
- **Objective:** The investigators of this study developed, validated, and clinically evaluated a rapid and scalable quantitative liquid chromatography with tandem mass spectrometry (LC-MS/MS) assay that targets the HDL proteome. Using this assay, they developed algorithms based on the HDL proteome to estimate CEC and risk of coronary artery disease (CAD).

Methods

- HDL particles were enriched from serum specimens by binding isotope-labeled apolipoprotein A-1; the resulting ApoA-I-associated particles were digested and analyzed by LC-MS/MS. Twenty-one HDL-associated proteins were monitored; correlation of these proteins with CEC, as measured by cell-based assay, was determined.
- The proteins that correlated with CEC were used to construct a multivariate regression model for CEC (pCE). The model was tested on measurements of 157 CAD patients and 74 matched controls.
- These cases and controls were used to adjust to model to predict CAD (pCAD); the new model was analytically validated and then tested in a case-control myocardial infarction (MI) study of 137 specimens.

Results

- The targeted LC-MS/MS analysis yielded 5 proteins (apolipoproteins A-I, C-I, C-II, C-III, C-IV; Spearman r=0.86) that were used in the pCE model.
- Median pCE was lower in specimens from patients with CAD than in those from healthy control individuals: 9.91% vs 10.20% per 4 hours (*P*=0.03).
- The pCAD model was applied to specimens from the MI study.
  - Differences in pCE were confirmed (median [IQR]: 10.66 [9.96-11.54] vs 11.15 [10.48-12.32]; *P*=0.015).
  - Furthermore, control individuals had lower risk scores than MI patients (median [IQR]: 0.36 [0.19-0.51] vs 0.51 [0.38-0.64]; *P*=0.001).

Conclusions

- The investigators developed a multiplexed, high-throughput LC-MS/MS assay for targeted proteins of the HDL proteome.
- This study showed that analysis of the HDL proteome can be used to estimate CEC, and that the CEC estimates are associated with CVD risk.
- These findings present new opportunities to examine the clinical utility of the pCE and pCAD models in larger populations.

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Webpage
https://www.msacl.org/view_abstract/MSACL_2019_US.php?id=719

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