

Racing for the True Metabolomics Signature of Coronary Artery Disease

Qureshi WT^{*} and Yeboah J

Division of Cardiovascular Medicine, Department of Internal Medicine, Wake Forest University School of Medicine, Winston Salem, NC 27105, USA

^{*}Corresponding author: Qureshi WT, Division of Cardiovascular Medicine, Department of Internal Medicine, Wake Forest University School of Medicine, Winston Salem, NC 27105, USA, Tel: 3367167015; Fax: 336 716 9188; E-mail: wqureshi@wakehealth.edu

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Editorial

Since the introduction of metabolomics in late 1990s, researchers have been looking for the holy grail of cardiovascular diseases using this approach [1,2]. However, despite several reports showing metabolomics markers successfully identifying coronary artery disease (CAD) [3,4], there is still lack of consensus on the true metabolomics signature of CAD.

Previous research has identified several metabolites related to gut microbiome [5-7], fatty acid metabolism [8], inflammation [9], steroid metabolism [10], sphingolipids [11], and phospholipids as biomarkers of CAD [11]. Many of these biomarkers were either not validated or could not be replicated in other cohorts. Most of these studies were also done on collected samples obtained several years ago in dissimilar cohorts. There is therefore an inherent bias in using them either as a derivative or validation cohort. Limited participants or samples in each cohort also sometimes prohibit dividing a cohort into derivative and validation sub cohorts for identifying the true metabolomics signature of CAD. Furthermore, it also remains unclear whether the identified metabolite associated with CAD is causal or just a bystander.

Below are some of the challenges that need to be overcome in Metabolomics-CAD studies:

Metabolome is ever changing entity and depends on the state of epigenome, genome, environment and diet. As a result, complex patterns emerge when supervised and unsupervised multivariate models are used to identify biomarkers. In several instances, many biomarkers are identified without knowing their functional importance. This complicates the finding as it leads to question if this biomarker is a chance finding or is truly related to the disease phenotype.

Most of these metabolites are isolated from cohorts of middle aged and older individuals that are usually on medications. Many of these medications affect the metabolome. These medicines affect metabolome depending on again the complex interactions among epigenome, genome, environment and diet.

Metabolomics studies mainly utilize urinary and plasma samples. Both represent the average of metabolic processes in the body. Using them to identify a disease of a specific organ is difficult as these metabolites are not specific to a particular organ. Most of the body's organs utilize similar metabolic processes and hence only a true systemic disease process could impact these metabolites. This is in contrast to proteomic biomarkers where proteins are much more organ and cell type specific e.g. troponin.

The metabolome changes with age. It is not entirely clear that what is actually related to age which changes the metabolism of the body. Cohorts with wide spectrum of age groups are not readily available to

study metabolomics of disease phenotypes. This may suggest that age specific metabolic biomarkers may be needed.

There are several methodology-based challenges which range from differences in techniques used for isolation of metabolites to methods to quantify metabolites such as use of mass spectrometry or nuclear magnetic resonance spectroscopy. Quality control is essential and internal standards are frequently run with the analytes.

Lastly, the statistical methods to identify metabolite biomarkers are still in their infancy. Due to high dimensionality of the data, methods that could select important analytes in correlated datasets are used. However, there is currently no acceptable method used for this purpose.

The enormous but unrealized potential of metabolomics could be achieved by focusing on challenges enumerated above. Addressing these challenges may ultimately produce a validated true metabolomics signature of CAD, an achievement which will greatly advance our knowledge on the pathophysiology of CAD and open up new avenues for treatment and prevention.

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