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## Health and Biomedical Pillar

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## Lipidomics for the Prediction of the Unstable Coronary Plaque

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Plaques that build up in the lining of the coronary arteries are made up of lipids, inflammatory cells, smooth muscle cells and connective tissue. Thrombosis of a not necessarily occlusive but unstable plaque most often causes episodes of unstable angina and myocardial infarction (MI). Preventing this sudden and adverse event seems to be the only effective strategy to reduce mortality and morbidity of coronary artery disease (CAD). Countries in the Middle East bear a heavy burden from cardiovascular disease. The population of Qatar is particularly prone to CAD with patients presenting with MI at a young age. The prevalence of CAD is in turn promoted by risk factors such as smoking, hypertension, dyslipidemia, diabetes and sedentary lifestyles. Metabolomics approaches to the identification of disease biomarkers rely principally on the comparative analysis of metabolite expression in normal and disease patients, animal models or cell cultures to identify aberrantly expressed proteins or concentration changes in metabolites that may represent new biomarkers or elucidate a disease mechanism. Lipidomics is the global identification and quantification of a diverse range of lipids in biological systems and is a subset field in metabolomics. The eukaryotic lipidome might comprise of 10,000 to 100,000 individual species of lipids originating from a few hundred lipid classes. These lipids are distributed as part of biological membranes, energy storage substances and sometimes function as signal transducers. Altered lipid metabolism and dyslipidemia in the context of inflammation and oxidative stress are driving forces in the transition from stable to unstable plaques. Therefore, a characteristic lipid signature within unstable human plaques and also in the circulating blood plasma could be a predictor of an oncoming cardiac event. This ongoing study was conducted on samples volunteered by acute coronary syndrome (ACS) patients at the Heart Hospital, Doha, Qatar. ACS is a term that describes any condition brought on by the sudden reduced blood flow to the heart due to thrombosis in the coronary arteries and encompasses unstable angina (UA) and both ST-segment elevation (STEMI) and non ST-segment elevation myocardial

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infarction (NSTEMI). A complete occlusive thrombi leads to extensive myocardial cell death and typically produces an elevated ST-segment in the electrocardiogram. In UA, ischemia occurs unpredictably and suddenly and is caused by the temporary formation of blood clots within the coronary arteries. Unstable angina often occurs before a MI. Distinguished from ACS are patients with stable angina (SA) who develop symptoms due to exertional ischemia. The aim of this study was to profile the global individual lipid levels of subjects in Qatar with unstable CAD, comparing global lipid levels between patients with unstable angina and ST-elevated myocardial infarction. We chose to discover the lipid biomarkers using a workflow utilizing tandem mass spectrometry with on-line ultra-high pressure liquid chromatography (UPLC-MS/MS). Mass spectrometry is a powerful technique that can be used to identify unknown compounds, to quantify known materials and to elucidate the structure and chemical properties of molecules. Recent advances in the accuracy and speed to the technology allow data acquisition for the global analysis of proteins, lipids and metabolites from complex samples such as blood plasma or serum. As we were trying to discover a new lipid biomarker, a technique that would maximise the number of compounds detected, identified and quantified them was favourable. Once the samples were analysed by tandem mass spectrometry, the ion intensity data from each sample was aligned with each other by retention time and lipid mass, normalised and deconvoluted. The signals were then attributed to a particular lipid species by utilising a lipid database and comparing the mass of the detected lipid and piecing together information gained from the fragment data of that lipid from the orbitrap. Statistical analyses of the signals for each individual lipid were then conducted by comparing within group percent coefficient of variation (%CV), fold change and analysis of variance (ANOVA) tests between sample groups and q-value and power calculations. Principal component analysis (PCA) was conducted in order to differentiate the samples under supervised conditions into STEMI and UA groups. A total of 1,663 and 874 lipid compounds were identified in positive and negative modes of mass spectrometry respectively. Of these, 7 compounds showed a significant change (ANOVA p-value < or equal to 0.001) between the STEMI and UA groups. The identities of these compounds are yet to be elucidated. Of the compounds with a significant change between sample groups of ANOVA p-value < or equal to 0.005, five compounds were able to be identified by mass and spectral matching with a lipid database. The PCA scores plot, which distributes samples in multi-dimensional space according to the variance seen in each principal component, showed very low evidence of discrimination between the sample groups with sample scores clustered in a single mixed pattern. This analysis suggests that the lipid abundance changes between the sample groups were difficult to find. This was most likely due to a combination of two reasons: (1) large within-group biological variance that needs to be overcome to detect the between-group variances and (2) the low differences in lipid concentrations between the sample groups. With a greater number of samples, this results is expected to change as the power of the study would increase. Successful results obtained from this study will aid healthcare professional in intervening with appropriate treatment in persons showing no symptoms but are under threat of developing angina or acute MI. The discovery of a lipid biomarker could assist healthcare professionals in prevention of an acute cardiac event thereby saving lives.