The Role of Lipopolysaccharide-Binding Protein in Coronary Disease Among Patients with Diabetes

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Introduction: Diabetes affects over 38 million Americans, with 1.2 million new cases diagnosed yearly. Patients with diabetes and obstructive coronary artery disease (OCAD) are 2-4x more likely to die from cardiovascular events even after glycemic control compared to non-diabetic population. Lipopolysaccharide binding protein (LBP) has been identified by prior research as a biomarker of obstructive coronary artery disease (OCAD). LBP has an established role in the inflammatory response and has been shown in prior studies to be associated with macrophage function along with surrogate markers of atherosclerosis. Our hypothesis is LBP is an independent predictor of obstructive coronary disease and elevated plasma levels are associated with heightened levels of macrophage driven inflammation.

Methods: Using diabetic plasma samples and paired clinical data from 70 patients from the CASABLANCA registry, univariate and multivariate logistic regression was performed to identify factors associated with LBP. Subsequently, we identified 75 plasma samples from diabetic patients from the UC Cardiovascular Biorepository and performed ELISA for measurement of LBP level. Clinical variables were extracted and adjudicated by two reviewers, after which this data was used to generate similar regression models. Regression models were adjusted for factors including history of hypertension, heart failure, myocardial infarction, peripheral artery disease, dyslipidemia, chronic kidney, and chronic obstructive pulmonary disease. Using a LBP knockout THP1 line along with control cells, macrophage activation was assessed following addition of plasma to THP1 cells using flow cytometry to evaluate CD80 expression. To further validate the impact of LBP on atherosclerosis, we are currently generating mouse lines ($LBP^{-/-}/LDLr^{-/-}$, $LBP^{-/-}$) which will be used for atherosclerosis studies. Following high fat diet, atherosclerotic plaque burden and composition will be assessed.

Results: Within the CASABLANCA cohort, Univariate linear regression analysis revealed LBP level was significantly associated with CAD ($p \leq 0.05$), hypertension ($p \leq 0.05$), and chronic kidney disease (CKD) ($p \leq 0.0055$). Multivariate regression identified CAD ($p \leq 0.05$), COPD ($p \leq 0.05$), and CKD ($p \leq 0.05$) as significant. Among the 75 samples analyzed from the UC Cardiovascular Biorepository, there was no significant difference ($p > 0.1$) between LBP levels from diabetic patients with or without CAD. Furthermore, there were no statistically significant predictors of LBP including coronary artery disease. There was not a statistically significant difference between macrophage activation between high and low LBP concentrations, although there was a trend in association of low LBP level with higher levels of macrophage CD80 expression. The mouse lines are still being established.

Conclusion: Within the CASABLANCA cohort, plasma levels of LBP were associated with HTN, CKD, and COPD. Mass spectrometry is superior to ELISA for accurate quantitation of plasma levels of LBP, which may explain why LBP was not a predictor defined LBP expression in plasma samples from our validation cohort. Low levels of plasma LBP caused more macrophage activation. We have successfully generated an LBP model on LDLr background which will be used for future studies to elucidate the role of LBP in atherosclerosis.

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