The Relationship of Inflammatory Cytokines (IL-6, IL-17A and TNF-α) to Co-morbidities of Cardiovascular Disease in a Large Community-based Patient Population

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Abstract

Background: Interleukin 6 (IL-6) and IL-17A (IL-6 and IL-17A) and Tumor necrosis factor-α (TNF-α) are inflammatory cytokines that may play a role in the pathogenesis of atherosclerosis. Previous studies have shown these cytokines to be in many areas of cardiovascular disease (CVD) including acute myocardial infarction, heart failure and coronary artery disease. We determined plasma levels of IL-6, IL-17A and TNF-α and identified the effect of co-morbidities on their levels in a large CVD risk study population.

Methods: Immunoassays for IL-6, IL-17A and TNF-α were developed using Single Molecule Counting Technology and validated in a CLIA licensed, CAP accredited laboratory (Singulex). The 95th percentile upper limit of normal (ULN) were 4.5, 1.9 and 2.5 pg/mL, and the precision profiles were 1.2%, 1.3% and 1.5% (RSD%) for IL-6, TNF-α, and IL-17A respectively. Blood samples were measured for cytokines, LDL, HDL and HbA1c in 21,327 community-based patients at risk for CVD. Cytokine and non-parametric analyses were performed in de-identified data using SAS v9.3 (p<0.05) considered significant.

Results: The characteristics of the inflammatory cytokines in a population at risk for CVD are shown in the Table. All three cytokines showed higher concentrations in older patients as well as those with CV risk factors of pre-diabetes, diabetes and HDL dyslipidemia. IL-6, TNF-α and IL-17A results were determined from 21,327 unique patients. The percent of patient results quantified were higher than those observed in healthy populations and coincide with risk factors for CVD.

Discussion

Elevated pre-inflammatory cytokines have been clearly demonstrated as risk factor for the development and worsening of CVD in numerous studies. Therefore, there is a need for high-sensitivity assays that can detect early signs of atherosclerosis. Immunoassays based upon high-sensitivity SMCT™ technology are capable of quantifying pre-inflammatory cytokines IL-6, TNF-α, and IL-17A in the plasma of nearly all healthy patients. For all cytokines, the percent of patients above the specific cytokine 95th%-tile increased for every age decade.

Conclusions

IL-6, TNF-α and IL-17A results were determined from 21,327 unique patients. The percent of patient results quantified above the assay LoD was 97.4%, 99.3%, and 90.1% respectively. The percent of patients above the assay 95th%-tile were 38.4%, 4.0% for IL-6, TNF-α, and IL-17A respectively. The median patient population distribution was significantly higher than the reference population for TNF-α (p<0.001), but not for IL-6 or IL-17A (p=0.1160 and p=0.1830 respectively). For all cytokines, the percent of patients above the specific cytokine 95th%-tile increased for every age decade, p<0.0001. Median TNF-α levels in men were slightly higher than women (2.5 pg/mL vs 2.4 pg/mL, p=0.001), however IL-6 and IL-17A did not have a gender difference (1.3 pg/mL vs 1.3 pg/mL, p=0.978 and 0.4 pg/mL vs 0.4 pg/mL, p=0.083 respectively). In a logistic regression model adjusted for hs-CRP, all three cytokines, age, gender, and BMI; IL-6 and TNF-α were significantly associated with elevated HbA1c (≥5.5%). All three cytokines were significantly associated with abnormal low HDL (<35 mg/dL or <45 mg/dL depending on gender) in a similarly controlled logistic regression model.

The percent of patients above the cytokine specific 95th%-tile was determined for IL-6, TNF-α, and IL-17A by age group (decade). Each cytokine significantly trended with age, p<0.0001.

References