Endothelial Microparticles and Systemic Complement Activation in Patients With Chronic Kidney Disease

Jason Bau
Kidney Research Centre, Ottawa Hospital Research Institute, Canada

Patients with chronic kidney disease are known to have a higher incidence of cardiovascular disease. While an element of this is due to the presence of traditional risk factors (such as hypertension), there remains a number of predisposing characteristics in this population that are poorly understood. One of these factors, is the idea that systemic inflammation is a marked contributor to cardiovascular outcomes and is hypothesized to be mediated by molecular pathways such as the complement system, among others.

However, the mechanism by which these pathways become activated remains unclear. One hypothesis is that microparticles, sub-micrometer cellular vesicles that are released by cells under times of duress, may be the missing link in this schema. Indeed, microparticles have been long known to be elevated in patients with chronic kidney disease (CKD) and patients on dialysis, as well as correlating with various other disease states such as diabetes and hypertension.

In this study, Jalal and colleagues hypothesized that microparticle formation may be a mechanism by which the complement pathway is activated in patients with known CKD. In this small, single-center trial, plasma and urine from healthy controls, patients with stage III/IV CKD and those having previously received a renal transplant but still having stage III/IV CKD, were examined for complement pathway activation. While a number of factors in this pathway were not dramatically changed between groups, the authors noted elevations in several factors specific to the alternative complement pathway, namely factor Ba and factor D.

Factor D is a serine protease which cleaves factor B into its catalytic (factor Bb) and non-catalytic (factor Ba) components. While traditionally, the alternative complement pathway is known for its role in opsonization of pathogens, there is a growing body of evidence that suggests that this pathway contributes to endothelial dysfunction and vascular injury. In support of this, plasma levels of factor Ba were inversely correlated with eGFR and positively correlated with urine albumin: creatinine ratios, suggesting an element of renal dysfunction. There was also a negative correlation between factor Ba levels and flow-mediated dilation of the brachial artery, an established measure for endothelial function, although this was no longer statistically significant after age adjustment (likely due to an underpowered study).

When examining endothelial microparticles from the three groups, levels of factor Ba and D were elevated in microparticles from patients with CKD. Furthermore, these microparticles could be used in vitro to activate the alternative complement pathway – again, suggestive of a functional role for microparticle-mediated endothelial dysfunction.

Despite being a relatively small sample size, their results are notable. Patients with CKD (stage III/IV),
regardless of transplant status, appear to have increased activation of the alternative complement pathway, mediated by factor-D containing microparticles, a novel linkage not previously identified. Furthermore, post-transplant medications (most of which target inflammatory pathways) did not appear to have any effect on measures utilized in this study. Although their findings of significance correlating factor Ba levels and artery flow-mediated dilation were lost after age adjustment, there was still a trend towards significance, highlighting the need for larger cohorts in follow up studies. What remains unclear is whether complement factor levels, or degree of pathway activation are correlated with adverse cardiovascular events – which could be achieved with longer follow-up duration and intermittent measures of complement factors. Nonetheless, the important findings in this study, raise more questions and highlight a novel role for microparticles in activation of the complement pathway.

REFERENCES


AUTHORS

Diana Jalal,MD; Brandon Renner,MS; Jennifer Laskowski, BS; Erik Stites,MD; James Cooper,MD; Karissa Valente, BA; Zhiying You, PhD; Loni Perrenoud, BS; Moglie Le Quintrc,MD, PhD; Ismaeel Muhamed, PhD; Uwe Christians, Phd; Jelena Klawitter, PhD; Margaret A. Lindorfer, PhD; Ronald P. Taylor, PhD; V. Michael Holers, MD; Joshua M. Thurman, MD doi: [10.1161/JAHA.117.007818]