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Serum levels of IL-6, IL-8 and IL-10 and risks of end-stage kidney disease and mortality

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A complex interplay of pro-inflammatory and anti-inflammatory cytokines likely affects the development and progression of chronic kidney disease (CKD). Specific cytokines include interleukin (IL)-6 and IL-8, which promote inflammation, and IL-10, which is generally considered to be anti-inflammatory [1]. We aimed to study associations of serum IL-6, IL-8 and IL-10 with the risk of incident end-stage kidney disease (ESKD) and all-cause mortality among participants of the African American Study of Kidney Disease and Hypertension (AASK). African Americans are at higher risk of ESKD, in part due to the prevalence of apolipoprotein L1 (*APOL1*) risk variants. Many suggest that a 'second hit' is required for kidney disease to develop in people with the *APOL1* high-risk genotypes [2, 3]. Inflammation may be a second hit. In *in vitro* studies, pro-inflammatory cytokines have been shown to increase APOL1 expression in endothelial cells and podocytes, two cell types found within the kidney [2]. In mouse models of *APOL1*, induced expression of the G1 and G2 risk variants was associated with azotemia, albuminuria and glomerulosclerosis [3]. Thus we also evaluated whether the cytokines IL-6, IL-8 and IL-10 modified the *APOL1*-associated risk for ESKD.

AASK enrolled African Americans with CKD [baseline iothalamate-measured glomerular filtration rate (GFR) 20–65 mL/min/1.73 m^2] attributed to hypertension [4, 5]. Individuals with diabetes were excluded. Our study population comprised 500 AASK participants with available baseline serum samples, of whom 333 had *APOL1* genotype data. We measured biomarkers using multiplex immunoassays (Meso Scale Diagnostics, Rockville, MD, USA). Interassay coefficients of variation were IL-6 5.05%, IL-8 5.09% and IL-10 6.72%. *APOL1* risk status was defined by a recessive genetic model (high risk, 2 risk alleles; low risk, 0–1 risk alleles) [6]. In Cox proportional hazards models we examined associations of baseline biomarkers (as $\log_2$-transformed continuous variables) with incident ESKD and all-cause mortality. Covariates included baseline age, sex, systolic blood pressure (BP), body mass index (BMI), smoking, GFR and urine protein:creatinine ratio (PCR). In sensitivity analyses, we further adjusted for randomized treatment groups and considered biomarkers as tertiles. Effect modification was assessed by additionally adjusting for *APOL1* risk status and European ancestry, with an interaction term between each biomarker and *APOL1* risk status ($n = 333$).

At baseline, median levels of IL-6, IL-8 and IL-10 were 1.29 pg/mL [interquartile range (IQR) 0.98–2.01], 17.26 (11.65–37.89) and 0.34 (0.25–0.46), respectively. Pearson's correlations among the three biomarkers were low (0.21 for IL-6 and IL-8, 0.13 for IL-8 and IL-10 and 0.08 for IL-6 and IL-10). Participants with higher IL-6 were more likely to be current smokers ($P = 0.03$), had higher mean BMI ($P = 0.002$) and had higher median urine PCR ($P = 0.04$) and high-sensitivity C-reactive protein ($P < 0.001$; Supplementary data, Table S1). Participants with higher IL-8 had higher mean systolic BP ($P = 0.02$; Supplementary data, Table S2), whereas participants with higher IL-10 had lower mean GFR ($P = 0.004$; Supplementary data, Table S3). The percentage of participants with *APOL1* high-risk status was similar across biomarker tertiles with the exception of IL-10 (32%, 17% and 30% in tertiles 3, 2 and 1, respectively; $P = 0.02$).

Over mean follow-up times of 7.4 and 8.8 years, there were 161 ESKD and 113 mortality events, respectively. In continuous analysis, IL-6 was not associated with ESKD or mortality. IL-8 was not associated with ESKD but was associated with a 26% greater risk of death (per 2-fold higher level) in the fully adjusted model. IL-10 was associated with a 28% greater risk of ESKD but was not associated with mortality (Table 1). Additional adjustment for IL-6 resulted in similar findings [hazard ratio for ESKD 1.30 (95% confidence interval 1.10–1.53)]. Adjustment for randomized treatment groups yielded comparable findings. Analysis by tertiles showed similar trends, with statistically significant associations between the top tertile

Table 1. Associations of biomarkers of immune activation with ESKD and all-cause mortality in AASK

Model	*n*	Events	IL-6		IL-8		IL-10	
			Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
ESKD								
Unadjusted	500	161	0.94 (0.80–1.11)	0.46	0.91 (0.81–1.03)	0.15	1.30 (1.13–1.49)	<0.001
Adjusted for age and sex	500	161	0.96 (0.82–1.13)	0.61	0.92 (0.82–1.04)	0.19	1.22 (1.07–1.39)	0.004
Further adjusted for systolic BP, BMI and current smoking	500	161	0.95 (0.81–1.12)	0.56	0.92 (0.82–1.04)	0.18	1.22 (1.07–1.39)	0.004
Further adjusted for GFR	500	161	0.85 (0.71–1.02)	0.08	0.94 (0.84–1.06)	0.32	1.26 (1.08–1.48)	0.004
Further adjusted for $\log_2$(urine PCR)	500	161	0.87 (0.73–1.05)	0.15	0.99 (0.88–1.12)	0.93	1.28 (1.09–1.51)	0.003
All-cause mortality								
Unadjusted	500	113	1.23 (1.04–1.45)	0.02	1.25 (1.12–1.40)	<0.001	1.14 (0.95–1.37)	0.17
Adjusted for age and sex	500	113	1.22 (1.03–1.45)	0.02	1.25 (1.12–1.40)	<0.001	1.20 (0.99–1.46)	0.06
Further adjusted for systolic BP, BMI and current smoking	500	113	1.17 (0.99–1.40)	0.07	1.22 (1.09–1.37)	0.001	1.20 (0.98–1.46)	0.07
Further adjusted for GFR	500	113	1.18 (0.99–1.42)	0.07	1.26 (1.12–1.41)	<0.001	1.17 (0.96–1.43)	0.12
Further adjusted for $\log_2$(urine PCR)	500	113	1.18 (0.99–1.42)	0.07	1.26 (1.12–1.41)	<0.001	1.17 (0.96–1.43)	0.12

Hazard ratios are per 2-fold higher baseline level of each biomarker.

and mortality for all biomarkers. None of the biomarkers modified the *APOL1*-associated risk for ESKD (P-interaction > 0.05 for all).

In summary, among African Americans with CKD attributed to hypertension, higher baseline levels of IL-8 were associated with a greater risk of death, while IL-10 was associated with ESKD. The association of IL-10 with ESKD, in particular, was surprising given its anti-inflammatory properties [1, 7, 8]. However, previous studies have also demonstrated associations between IL-10 and adverse outcomes, including acute kidney injury following cardiac surgery [9] and cardiovascular events among individuals with CKD [7]. Thus higher levels of IL-10 may be a proxy for ongoing inflammation. Consistent with our study, higher baseline levels of IL-6 in the Chronic Renal Insufficiency Cohort were not significantly associated with kidney function decline after accounting for baseline albuminuria [10]. Perhaps IL-6 is not a specific biomarker for worsening kidney function in patients with extant CKD.

Among critically ill patients with acute kidney injury, higher baseline levels of IL-8 have been associated with greater risk of in-hospital mortality [1]. Although inflammation has been shown to increase APOL1 expression [2, 3], we did not find any evidence of IL-6, IL-8 or IL-10 modifying the association of *APOL1* high-risk status with ESKD, perhaps due to limited power. The strengths of our study included a prospective study design, availability of *APOL1* genotypes and consideration of multiple biomarkers. The limitations are a relatively small sample size, particularly for the assessment of interaction with the *APOL1* genotype, potential for residual confounding and baseline measurements only. In conclusion, higher baseline levels of IL-8 and IL-10 in African Americans with hypertension-attributed CKD conferred greater risks of mortality and ESKD, respectively, whereas only the top tertile of IL-6 was associated with mortality. Further investigation is needed to evaluate whether anti-inflammatory therapeutics may slow the progression of CKD.

SUPPLEMENTARY DATA

Supplementary data are available at ndt online.

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DATA AVAILABILITY STATEMENT

The data underlying this article will be shared on reasonable request to the corresponding author.

CONFLICT OF INTEREST STATEMENT

C.R.P. is a member of the advisory board of Renalytix AI and owns equity in the same. C.R.P. serves on the Data Safety and Monitoring Board of Genfit. The other authors report no conflicts of interest.

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Serum potassium laboratory reference ranges influence provider treatment behaviors for hyperkalemia

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The prevalence of hyperkalemia in hospitalized patients ranges between 1 and 10% [1] and treatment commonly commences when serum potassium is 5–6 mEq/L [2–4]. Aside from certain cardiovascular diseases [3, 5], the risk of adverse events with serum potassium <5.5 mEq/L is low [2] and treatment has not been shown to mitigate the risk [3]. Serum potassium results are typically reported along with reference ranges, with abnormal results flagged and highlighted. While hyperkalemia treatment guidelines have not changed, laboratory reference ranges have. These ranges are largely based on updates aimed at incorporating a 95% reference population rather than considering adverse event data [6]. Our objective was to discover what effect a reference upper limit change for serum potassium has on provider treatment behavior for emergency department and hospitalized patients with hyperkalemia.

We performed a retrospective cohort study of all emergency department and hospitalized patients with an order for sodium polystyrene sulfonate (SPS; trade name Kayexalate) at 14 hospitals in a large New York, USA, health system between 2012 and 2018. The reference upper limit for serum potassium changed from 5.1 to 5.3 mEq/L on 23 December 2015. Data were collected from the enterprise electronic health record (EHR; Sunrise Clinical Manager, Allscripts, Chicago, IL) database and included serum potassium results most proximate to an SPS order (up to 12 h prior) and the associated laboratory reference upper limit for that result. We compared SPS ordering patterns