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Elevated histone-DNA complex level is associated with CKD progression: Results from CMERC-HI

Young Su Joo[1], Jwa-Kyung Kim, Ye Eun Ko[3], Shin-Wook Kang[3], Sungha Park[4], Tae-Hyun Yoo[3]
[1]Department of Internal Medicine-Nephrology, Yongin Severance Hospital, Korea, Republic of
[2]Department of Internal Medicine-Nephrology, Hallym University Sacred Heart Hospital, Korea, Republic of
[3]Department of Internal Medicine-Nephrology, Severance Hospital, Korea, Republic of
[4]Department of Internal Medicine-Cardiology, Severance Hospital, Korea, Republic of

Objectives : Previous studies evidenced that neutrophil extracellular traps (NETs) have causative roles in endothelial dysfunction in chronic inflammatory disease. However, the presence of NETs in CKD patients and their association with CKD progression have not been adequately evaluated. Here, we evaluated the association between histone-DNA complexes (nucleosome) level, as a surrogate marker of NETs, and CKD progression in patients with CKD.
Methods : Patients with CKD among the Cardiovascular and Metabolic disease Etiology Research Center-High risk study (CMERC-HI) study participants were examined. Key exclusion criteria were kidney failure with replacement therapy (KFRT) and preserved kidney function without proteinuria. Nucleosome and P-selectin levels were quantified using ELISA kit. Participants were categorized according to baseline nucleosome levels (Quartiles 1-3 and Quartile 4) and CKD progression was compared between these groups. The CKD progression was defined as a composite of halving eGFR from baseline value or onset of KFRT.
Results : A total of 756 participants were assessed, the mean age was 58.3 ± 12.6 years and 55.0% were male. During a total follow-up of 4,024 person-years (median 6.0 years), the composite outcome occurred in 288 (38.1%) participants among the CMERC-HI participants. In crude Cox regression, participants with elevated nucleosome levels (Quartile 4) showed a significantly high risk of CKD progression compared to those in Quartiles 1-3 (hazard ratio [HR], 1.47; 95% confidence interval [CI], 1.13-1.91). Similar elevated risk in elevated nucleosome was observed even after adjustment of age, sex, DM, SBP, eGFR, and proteinuria (HR, 1.36; 95% CI, 1.02-1.79). The nucleosome levels did not correlate with eGFR (Pearson correlation coefficient=0.009, P=0.79) but they showed a significant correlation with P-selectin levels (Pearson correlation coefficient=0.090, P=0.01).
Conclusions : Presence of NETs is associated with an increased risk of CKD progression. Elevated nucleosome levels correlated with P-selectin, suggesting that NETs may contribute to kidney injury through endothelial dysfunction.