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Effects of Uremic Serum on Endothelial Cell Damage is Mediated by Excessive Neutrophil Extracellular Trap Formation

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Objectives: Chronic kidney disease (CKD) is characterized by a progressive loss of renal function through the accumulation of uremic toxins leading to chronic inflammation. Cardiovascular (CV) disease is the leading cause of death in patients with chronic kidney disease (CKD) and endothelial dysfunction may be a key CKD-specific risk factor; however, the mechanism by which uremia influences endothelial dysfunction is still unclear. We report a role for excessive neutrophil extracellular trap (NET) formation induced by uremic serum on endothelial cell (EC) injury.

Methods: Plasma nucleosome and myeloperoxidase-DNA, representative markers of *in vivo* NETs, and the intracellular adhesion molecule (ICAM)-1 level were measured in hemodialysis (HD) patients and healthy volunteer (HV), and their prognostic role was evaluated. For *in vitro* study, we differentiated HL-60 cells into neutrophil-like cells (dHL-60) by applying retinoic acid, and the effect of uremic serum on dHL-60 and ECs were determined.

Results: The amount of *in vivo* NETs were significantly higher in incident HD patients compared to HV, and the markers were strongly associated with ICAM-1. In particular, nucleosome and ICAM-1 levels were independent predictors of a composite endpoint, all-cause mortality or vascular access failure. *In vitro*, HD-derived serum showed significantly increased NETs formation from dHL-60, and these NETs decreased EC viability and induced apoptosis. In addition, the ICAM-1 level in HUVEC supernatant was significantly increased by uremic serum-induced NETs compared to control serum-induced NETs.

Conclusions: Dysregulated neutrophil activities in the uremic milieu may play a key role in vascular inflammatory responses. The high mortality and CV complication rates in ESRD can be explained in part by excessive NETs formation, followed by EC damage and dysfunction.