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Effect of End Stage Renal Disease (ESRD) and Hemodialysis (HD) on Toll-like Receptor (TLR) Expression and Activities

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Introduction : ESRD is associated with inflammation, impaired immunity and increased susceptibility to bacterial infections. TLRs consist of a group of receptors which recognize structural patterns of molecules expressed on infectious microorganisms. TLRs are known to play an essential role in the innate immune process involving granulocytes, monocytes and macrophages. HD with high-flux dialyzers frequently results in the influx of endotoxin fragments from dialysate to blood compartment. Recognition of these products by TLRs, expressed on circulating leukocytes and tissue macrophages, can lead to production and release of pro-inflammatory cytokines, chemokines, and adhesion molecules. These events can, in turn, contribute to non-infectious inflammation and oxidative stress which are constant features and major mediators of cardiovascular and numerous other complications of ESRD.

Object : This study tested the hypothesis that increased susceptibility to infections or alternatively the prevailing inflammatory state in the ESRD may be due, in part, to defective expression or funtion of the TLRs. Methods: 21 ESRD patients and age-matched controls were studied. Blood samples were obtained before and after HD and processed for TLR2 and TLR4 expressions in circulating granulocytes and monocytes by flow cytometry. In addition, blood samples were incubated with lipopolysaccharide (LPS, TLR4 ligand) and peptidoglycan (TLR2 ligand) for 24 hours to assess TNF-α, IL-1 and IL-6 production by ELISA.

Results : TLR2 and TLR4 expressions in granulocytes and monocytes of ESRD patients were not significantly different from those of the controls. Likewise 3-hour HD procedure did not significantly change expression of TLRs. Stimulation with LPS resulted in a significantly higher IL-6 and TNF-α production in the ESRD patients than in the controls ($p<0.05$). However, response to stimulation with peptidoglycan was similar in the two groups.

Conclusion : TLR2 and TLR4 expression in peripheral granulocytes and monocytes are not significantly altered in stable ESRD patients treated with chronic HD. However, TLR4 activation by LPS results in a supernormal production of pro-inflammatory cytokines in ESRD patients. This may contribute to the pathogenesis of inflammatory state and its untoward consequences in HD-treated ESRD patients. The mechanism for the exaggerated response to LPS stimulation is uncertain and awaits further investigation.