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Role of CRP and IL-18 exon 4 (105 A/T) Polymorphism in Inflammation and Pathogenesis of Type 2 Diabetic Nephropathy

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Abstract

Background
Diabetic nephropathy (DN) is the leading cause of chronic kidney failure worldwide and most significant long-term complications in terms of morbidity and mortality in ~40% of type 2 diabetic nephropathy patients (Type2 DN). Type2 DN is frequently associated with an acute-phase reaction, suggestive inflammatory response involved in renal vascular disease process. The acute phase reactant CRP (C-Reactive Protein) is a marker of systemic inflammation regulated by cytokines. Evidence suggests that immune cells participate in renal vascular injury and increased glomerular interstitial infiltration of macrophages/ monocytes induces inflammation in Type2 DN. Apart from immune cells, renal endothelial, epithelial, mesangial, and tubular cells are capable of synthesizing proinflammatory cytokines such as interleukin-18 (IL-18). IL-18, a major pro-inflammatory cytokine belonging to the IL-1 cytokine super-family, is mainly produced by activated macrophages. It can regulate both innate and adaptive immune responses through its effects on enhancing lytic activity of NK-cells, monocytes, dendritic cells, T cells, and B cells in the affected areas and its expression is increased in the inflammatory sites and plays a pivotal role in development and progression of type 2 DN towards ESRD. IL-18 polymorphic gene variants may modulate cellular response and contributes to inter individual variation among in Type2 DN patients.

Objective
The present study was undertaken to estimate serum CRP levels and analyse polymorphic variants of IL-18 exon 4 (105 A/T) involved in pathogenesis of Type2 DN.

Methods
The study population consisted of 200 patients with Type 2 DN and an equal number of age and gender matched healthy controls. Blood samples were collected from South Central Railway Hospital, Lallaguda, Secunderabad. Informed written consent was obtained from all the subjects. Serum CRP levels were estimated based on the principle of latex agglutination described by Singer and Plotz. Genotyping of IL-18 exon 4 (105 A/T) polymorphism was done by PCR-RFLP method.

Results
The mean serum levels of CRP in T2DN was found to be significantly high when compared to control group ($p<0.01$). Genotypic analysis of IL-18 exon 4 (105 A/T) polymorphism analysis found that TT genotype was significantly high in T2DN patients and confers 2-fold risk for the development of disease in codominant, dominant and recessive models against the progression of Type2 DN.

Conclusion
Our data suggest the importance of CRP and that TT genotype of IL-18 exon 4 (105 A/T) polymorphism as a risk factor for the susceptibility for Type 2 DN.

Keywords: Diabetic nephropathy, C-Reactive Protein, Interleukin-18.

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