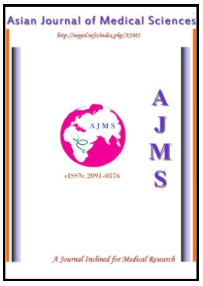
Asian Journal of Medical Sciences 2 (2011) 46-48

ASIAN JOURNAL OF MEDICAL SCIENCES



Strong relationships between inflammation, atherosclerosis and end stage renal disease

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Abstract

End-stage renal disease (ESRD) is characterized by an exceptional mortality rate, much of which is the result of cardiovascular disease (CVD). Although traditional risk factors are common in ESRD patients, they may not be sufficient alone to account for the high prevalence of CVD in this condition. Recent evidence demonstrates that chronic inflammation is a common feature in ESRD patients and it may cause malnutrition and progressive atherosclerotic CVD by several pathogenetic mechanisms. The causes of inflammation in ESRD are multifactorial and, while it may reflect underlying CVD, an acute-phase reaction may also be a direct cause of vascular injury by several pathogenetic mechanisms. There is strong evidence that inflammatory markers are closely linked to ESRD. There seems to be a strong evidence of inflammatory markers, inflammation and atherosclerosis in ESRD patients and it is likely that proinflammatory cytokines and the genetic polymorphism in these cytokines may be important players in this scenario.

Key Words: Cytokines; ESRD; Inflammation; Polymorphisms; CVD

1. Introduction

The diabetic nephropathy, hypertension followed by cardiovascular disease (CVD) remains the main causes of morbidity and mortality in patients with end-stage renal disease (ESRD). The annual mortality rate due to CVD is 9%, which is 10 to 20 fold higher than in the general population, even when adjusted for age, gender, race and diabetes mellitus.[1] The death rate among ESRD patients with signs of inflammation, malnutrition and atherosclerosis are similar to what one finds in many patients with metastatic malignancy.[2] The causes of atherosclerotic CVD in ESRD patients are probably multifactorial. Classic risk factors such as dyslipidaemia, hypertension and smoking are prevalent in many patients with ESRD, but studies have shown that excess CVD is not explained adequately by traditional risk factors.[3] Thus, it has been postulated that non-traditional risk factors, such as oxidative stress and inflammation, may be more important.[4] Over the last years, the idea that inflammation plays a key role in atherosclerosis has received much attention[5] and, based on findings in non-renal patient groups, it is evident that inflammation may also be a contributor to cardiovascular morbidity and mortality in ESRD patients.

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2. Discussion

C-reactive protein (CRP) is a precise objective index of the inflammatory activity and that it accurately reflects generation of pro-inflammatory cytokines, such as interleukin (IL)-6 and tumour necrosis factor-a (TNF-a). Accordingly, elevated serum levels of pro-inflammatory cytokines have also been demonstrated to be associated with increased mortality in dialysis patients.[6] As elevated CRP has been shown to be such a strong predictor of cardiovascular mortality[7], available data suggest that the association between inflammation and atherosclerosis is particularly strong in dialysis patients.

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evidence of inflammatory markers, inflammation and atherosclerosis in ESRD patients and it is likely that proinflammatory cytokines and genetic polymorphism may be important players in this scenario.

All available evidence suggests an up-regulated pro-inflammatory cytokine system activity in ESRD patients, and markedly elevated levels of cytokines have been found both before and after the start of dialysis treatment.[8] The cause(s) of elevated serum levels of pro -inflammatory cytokines in ESRD patients are not well understood, although both decreased renal clearance and increased cytokine production are likely to contribute. Different genetic variants are known which involved in this patho-physiology are *IL-6, IL-4, TNF-a, IL -1 gene cluster* and *ICAM-1* and the polymorphism in cytokine genes may influence the prevalence of inflammation and morbidity in ESRD. *TNF-a* is involved in the initiation and progression of renal injury in chronic kidney disease. Elevated plasma *TNF-a* concentration is frequently found in patients with chronic renal failure and correlates with their mortality. *IL-4* is shown to have multiple functions in the immune response. It modulates the immune response affecting the variety of cell types. It inhibits the release of inflammatory mediators such as *TNF a, IL-6* and *IL-1*. It regulates the differentiation of precursor T helper cells into those of the Th2 subset and is an important regulator of IgG isotype switching.[9] *Interleukin-6* is a pleiotropic cytokine with both pro and anti-inflammatory properties depending on which cell system is involved. It is secreted mainly by macrophages. It mediates the stimulation of the acute phase response and the activation and differentiation of macrophages, B-cells and T-cells. *IL-6* derived from antigen presenting cells inhibits the differentiation of naïve $CD4^+$ T cells into Th1 cells. *Intercellular adhesion molecule-1 (ICAM-1)* (CD 54) is a leukocyte adhesion molecule which is expressed at high levels in the normal kidney on the endothelial cells and interacts with $ß_2$ integrins. It is involved in leukocyte adhesion and also enhances the activation of T helper cells. These genetic variants may produce two types of phenotype, based upon their expression these may be low producing and high producing genotype. An imbalance in this alters the production of cytokine in blood, hence due to inflammation there may be CVD in ESRD patients. A study reported by Ranganathan et al[10] the high producers of *IL-4* and low producers of *IL-6* genotypes showed ~6 fold risk. And the risk was also seen in low *IL-4* and low *IL-6* combinations. Further in case of TNF-*a,* the combined analysis of high producing phenotype of TNF- *a* gene showed susceptibility towards ESRD, while low producers revealed protective effect.[10]

Although the association between CVD and inflammation in the dialysis patient population is well documented, we do not know if the acute-phase response merely reflects an epiphenomenon accompanying established atherosclerotic disease or whether different proinflammatory markers are involved in the initiation and/or progression of atherosclerosis. It should be emphasized that pro-inflammatory cytokines may also have direct atherogenic effects per se. For an example, TNF-a has been shown to mediate endothelial dysfunction, down-regulate ApoE secretion and promote in vitro calcification of vascular cells.[9] Also, IL-6 may have independent atherogenic properties. The association between chronic inflammation and CVD may also be indirect, as chronic inflammation has been shown to be associated with endothelial dysfunction, insulin resistance and increased oxidative stress, all believed to cause atherosclerosis.[11]

3. Conclusion

The data suggest that polymorphism in pro-inflammatory cytokines together with their production in blood pro-inflammatory cytokines play a central role in the genesis of CVD in ESRD patients. Thus, it could be speculated that suppression of the vicious cycle of inflammation and atherosclerosis would improve survival in dialysis patients. As there is as yet no recognized or proposed treatment for ESRD patients with chronic inflammation, it would be of obvious interest to study the long-term effect of various anti-inflammatory treatment strategies and cardiovascular status as well as the outcome in these patients. The present study revealed a greater risk with several risk alleles of *IL-6, IL-4, TNF-a* and *ICAM-1* and suggests that gene-gene interaction may contribute to a causal propensity for developing ESRD.

Acknowledgements

We are thankful to Department of Biotechnology, Government of India for financial support. GT is thankful to the Jawaharlal Nehru Memorial Fund, New Delhi, for awarding junior research fellowship.

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