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Inflammatory Agents and Systems in Diabetic Nephropathy Pathogenesis

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Short communication

It is widely accepted that chronic inflammation is profoundly involved in the development of atherosclerosis. Adhesion molecules, pro-inflammatory cytokines and chemokines, including soluble intercellular adhesion molecule-1 (sICAM-1), inter leukin-18 (IL-18) and monocyte chemotactic protein-1 (MCP-1), are involved in the pathogenesis of diabetic nephropathy as well as atherosclerosis. C-reactive protein (CRP) is a good marker for cardiovascular risk4, and is a precipitating factor for diabetic nephropathy. Angiotensin II, which is produced by the Renin–Angiotensin System (RAS), is known to promote inflammation6.

Inhibition of the RAS and associated inflammation might be Reno protective in chronic renal diseases, including diabetic nephropathy. Oxidative stress is a critical pathogenic component of atherosclerosis and diabetic nephropathy. After the onset of renal disorders, the levels of pro-inflammatory cytokines and oxidative stress begin to increase, inducing cardiovascular diseases through vascular endothelial dysfunction. Furthermore, an increase in oxidative stress has been reported in hyperglycemic rats.

While activation of the RAS increases oxidative stress, angiotensin-converting enzyme inhibitors (ACEI) and angiotensin II type 1 receptor blockers (ARB) inhibit oxidative stress. Combination therapy with an ACEI and an ARB has been considered in several renal diseases to protect the kidney by potently inhibiting RAS activity. In the context of diabetic nephropathy combination therapy was found to reduce albuminuria. However, most of the studies testing ACEI/ARB combination therapy in diabetic nephropathy were short-term observational studies, and clinical studies attempting to elucidate the mechanisms underlying these Reno protective effects are not sufficient.

In patients with diabetic nephropathy, ACEI/ARB combination therapy is expected to have more potent anti-inflammatory and anti-oxidative stress effects than monotherapy at the systemic and local levels in the kidney. Combination therapy might also inhibit the development or progression of atherosclerosis and diabetic nephropathy more potently than monotherapy. However, to our knowledge, no clinical studies have evaluated the anti-inflammatory and anti-oxidative stress effects of combination therapy. Therefore, we carried out a randomized controlled study of ACEI/ARB combination therapy *vs.* ARB monotherapy in patients with type 2 diabetes and early nephropathy to compare the anti-inflammatory and anti-oxidative stress effects of these therapies.

Diabetic nephropathy, a major microvascular complication of both type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM), is an important cause of end-stage renal disease in Western nations. This complication was traditionally thought to result from interactions between hemodynamic and metabolic factors.1 However, current knowledge indicates that the extent of renal damage in patients with diabetes mellitus is not completely explained by increased systemic and intraglomerular pressure secondary to hemodynamic and metabolic factors, or by the modification of molecules under hyperglycemic conditions.

Clear evidence indicates that the pathogenesis of diabetic nephropathy is multifactorial; both genetic and environmental factors are responsible for triggering a complex series of pathophysiological events. A growing understanding of the complex interactions between these factors has revealed several intricate mechanisms by which renal insults (including hemodynamic and metabolic changes) translate to functional and structural kidney injury in patients with diabetes.

Research during the past 10 years has provided insight into the etiology of diabetic nephropathy at the cellular and molecular level, and inflammation has emerged as being a key pathophysiological mechanism. Inflammatory molecules and mediators are, therefore, important in the early stages of diabetic kidney disease. Understanding the key features of inflammatory mechanisms involved in the development and progression of diabetic kidney injury will enable the identification of new potential targets and facilitate the design of innovative anti-inflammatory therapeutic strategies.

This Review will explore the hypothesis that the pathogenesis of diabetic nephropathy is associated with the inflammatory process. We focus on pro-inflammatory molecules and pathways related to the development and progression of renal injury, discuss the potential clinical use of inflammatory markers as predictors of diabetic nephropathy, and comment upon potential new strategies to treat diabetic nephropathy using agents that target these inflammatory pathways.

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