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Diabetic nephropathy and inflammation

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Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia due to insulin secretion or action defects. The prevalence of this disease is increasing rapidly worldwide and is becoming one of the major health problems.[1] Complication of diabetes includes microvascular and macrovascular. An example of a microvascular complication is diabetic nephropathy or diabetic kidney disease. Diabetic nephropathy can occur in 30-40% of patients with type 1 and type 2 diabetes mellitus.[2] Various factors have been involved in the pathophysiology of diabetic nephropathies, such as hemodynamic and metabolic changes, oxidative stress, activation of the renin-angiotensin system, and most recently, the role of the inflammatory process involved that can lead to disease progression.[3]

Inflammatory factors are increasingly recognized and developed after discovering histopathological features in macrophage infiltration, which correlates with disease progression in chronic renal failure. Moreover, inflammatory biomarkers correlate with end-stage renal disease mortality in diabetic nephropathy patients. The inflammatory process that characterizes the condition of diabetic nephropathy involves multiple molecular pathways, subclinical and chronic.[4,5] Biochemical stimuli resulting from hyperglycemia, and hyperlipidemia, including oxidative stress, lipid oxidation, glycated protein, and reactive oxygen species, initiate this process.[5] Glycated protein can also directly activate the complement system and initiate pro-inflammatory signals. The activation of this innate immune damage sensor causes responses of renal endothelial cells, mesangial cells, and podocytes producing various inflammatory cytokines, chemokines, and adhesion molecules.[4,5] These inflammatory molecules then attract and activate monocytes and macrophages, leading to the next inflammatory response cascade. The activity of these renal cells and innate immune cells causes persistent chronic inflammation that results in extracellular matrix deposition and fibrosis.[5,6]

Studies on biomarkers of diabetic nephropathy have been widely conducted, demonstrating the role of inflammation in initiating or predicting the development of albuminuria in patients with type 2 diabetes mellitus or diabetic nephropathy.[7–9] Genomic and transcriptomic studies also discovered new biomarkers. In a recent study, RNA-seq using a matched donor and patient biopsy tissue fraction demonstrated an inflammatory response, complement activation, and ECM deposition as key pathophysiological processes in diabetic nephropathy.[10] A clinical trial of new anti-inflammatory therapies in patients with diabetic nephropathy demonstrated improvements in outcome biomarkers but not consistent benefit in renal outcomes.[11] The presence of side effects on the kidneys due to nonsteroidal anti-inflammatory drugs can exemplify the causes of this inconsistency.[12] The latest conceptual model was developed to identify and assess newly discovered drugs using five components of renal function, comprising immune cell withdrawal and activation, filtration, resorption and secretion, ECM regulation, and perfusion.[13]

Based on the elucidation above, it is concluded that the inflammatory process is a factor that plays a role in the development of diabetic nephropathy by involving many molecular pathways. These factors suggest that the development of new drugs needs to be based on the inflammatory process, the need for a more appropriate approach to maximize health outcomes, and a strong new understanding of the

pathophysiology of diabetic nephropathy.

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