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## Role of oxidative stress and inflammatory cytokines in renal injury

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Renal injury caused by oxidative stress and inflammatory cytokines is one of the most important causes of chronic renal disease and renal failure. An increase in the level of inflammatory cytokines, such as tumor necrosis factor-alpha (TNF- $\alpha$ ), interleukin-6 (IL-6), and transforming growth factor-beta (TGF- $\beta$ ), and the reduction of the level of these two oxidative stress indexes, superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), and enhancing malondialdehyde (MDA) expression have shown that inflammatory mediator and oxidative stress are responsible for developing nephropathy by raising the invasion of inflammatory cell, hypertrophy with vacuolar degeneration leading to renal tubular cells apoptosis.

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In recent years, we have seen a significant increase in renal diseases throughout the world (1). Disruption of the balance of oxidants and antioxidants is the result of oxidative stress. In the majority of cells, glutathione peroxidase (GSH-Px), catalase (CAT) and superoxide dismutase (SOD) are endogenous enzymes due to oxidative stress (2,3). Free oxygen radicals cause lipid peroxidation leading to cellular membrane, mitochondrial degradation and cell death (4). Kidney inflammation and fibrosis-induced oxidative stress result from reactive oxygen species (ROS) production that leads to redox-sensitive pro-inflammatory signal transduction pathways. Chronic kidney disease is a result of overproduction of ROS and NAD[P]H oxidase, down-regulation of antioxidants enzyme and antioxidant pathways impairment and Nrf-2 (5,6). Diabetic nephropathy (DN) caused by oxidative stress is one of the most important causes of chronic kidney disease and renal failure. Although the exact cause is still unknown, previous studies have shown that ROS play an important role in diabetic kidney disease via inhibiting the production of nuclear factor erythroid-2-related

factor 2 (Nrf2). Nrf2, a transcription factor, which has an important antioxidant role in oxidative stress situation and also increasing glucose level (7-9), decreases the level of antioxidant and causes mitochondrial and cellular membrane damage and rises apoptosis (10). In diabetic kidney disease, Sha et al observed not only an increase in the level of Bax and caspase-3 but also a decrease in Bcl-2. Moreover, an increase in the level of inflammatory cytokines, such as tumor necrosis factor-alpha (TNF- $\alpha$ ), interleukin-6 (IL-6), transforming growth factor-beta (TGF- $\beta$ ), and the reduction of the level of these two oxidative stress indexes, SOD, GSH-Px, and enhancing malondialdehyde (MDA) expression have shown that inflammatory mediator and oxidative stress are responsible for developing diabetic kidney disease by raising the invasion of inflammatory cell, hypertrophy with vacuolar degeneration leading to renal tubular cells apoptosis (11). Several studies have reported that superoxide anion, hydroxyl radicals and hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) are a variety of oxygen free radicals responsible for a significant part of kidney damage. Furthermore, GPx, GR, CAT

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and SOD are intracellular antioxidant enzymes that play important roles in the protection of kidney against oxidative damage (12). Several studies have indicated that oxidative stress plays an important role in the development of various disorders such as renal diseases through the activation of intracellular signaling response and creating systemic responses that lead to kidney damage (13,14). The mechanism of post-transplant hypertension in animals and humans renal transplantation is related to oxidative stress. Angiotensin II (Ang II) increases the level of oxidative stress and ROS through enhancing NADPH production that could elevate the expression of p22phox, a 22-kDa  $\alpha$  subunit of cytochrome b558 that leads to superoxide anion radical (O<sub>2</sub><sup>-</sup>) production. It can also reduce nitric oxide (NO) bioavailability. NO depletion raises sodium secretion and renal vascular resistance, and also reduces renal blood flow and glomerular filtration rate (GFR). O<sub>2</sub> destroys NO by converting it into peroxynitrite (15,16). Kidney damage, which is a result of oxidative stress formation, causes cell components destruction, such as proteins, lipids, lipoproteins, and DNA and cellular membranes. Renal function and the development of kidney injury are related to microRNAs (miRs) that lead to the regulation of gene expression via binding to the 3'-UTR of their target mRNAs. MiR-423-5p inhibits cellular repairmen via producing oxidative stress and inhibiting glutathione S-transferase Mu 1(GSTM1). Moreover, the depletion of GSTM1 increases oxidative stress production (17). Renal ischemia-reperfusion injury occurs in several clinical conditions, like hypovolemia after kidney transplantation. Ischemic reperfusion causes kidney damage via producing ROS, apoptosis and necrosis. There is an important relationship between Bax and Bcl-2 with cellular apoptosis. Bax and caspase-3 raise cellular apoptosis by increasing the number of free radicals, intracellular Ca<sup>2+</sup> emission and altering the mitochondrial permeability (18). ROS cause inflammation in kidney through the activation of NF- $\kappa$ B signal pathway. Likewise, NF- $\kappa$ B raises the level of proinflammatory mediators and the imbalance of "Th1/Th2 drift" (Th, helper T cell). Previous studies have shown that Th1/Th2 imbalance is associated with various kidney damages (19).

Overproduction of cytokines and chemokines including TNF- $\alpha$ , nuclear factor- $\kappa$ B (NF- $\kappa$ B), monocyte chemoattractant protein-1 (MCP-1), IL-6, and IL-1 $\beta$  causes inflammatory cells activation, and also produces cytotoxic ROS that are responsible for causing septic acute kidney injury and renal damage (20).

#### Authors' contribution

RMK and PAB prepared the primary draft. AH edited and finalized the manuscript. All authors read and signed the final paper.

#### Conflicts of interest

The author declared no competing interests.

#### Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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