Oxidative stress in the pathogenesis of diabetic nephropathy
N Agrawal, S Singh, N Singh, S Kalra, G Srivastava

INTRODUCTION
Diabetic nephropathy is the leading cause of end stage renal diseases, and is a significant cause of morbidity and mortality in persons with diabetes.

While multiple pathophysiologic mechanisms contribute to the development of diabetic nephropathy, there is ample evidence to implicate oxidative stress and gluco-oxidative stress in the pathogenesis of this complication. Oxidative stress is created by various molecules, such as reactive oxygen species (ROS) and reactive dicarbonyl species, which result in renal damage through different mechanisms.

The sources of oxidative stress, i.e. ROS and reactive dicarbonyl in diabetes have been discussed earlier (1). This review focuses on the actions and pathways that these species take to create renal damage in diabetes.

RODOS REACTIONS
Diabetes nephropathy is characterized by glomerular mesangial expansion, due to deposition of extracellular matrix (2). This occurs because of both increased synthesis and reduced degradation of extracellular matrix proteins (ECMs), and is mediated by the high concentrations of glucose, Ang II, extracellular AGE proteins and a thromboxane analogue. These factors have been studied both in vitro and in vivo. (1)

All these factors stimulate cell signaling pathways which increase transforming growth factor-β (TGF-β) in the matrix protein. This is done via ROS generation. ROS is derived from NADPH oxidase activation, and also from the mitochondria (3). NADPH oxidase is activated by activation of protein kinase C (3), and vice versa (4).

ROS generation has been shown to increase in mitochondria in response to hyperglycemia, Ang II and AGE (3). Inhibitions of NADPH oxidase suppress the increase in TGF-β and extracellular matrix proteins (3). The same phenomenon is noted with inhibitors of mitochondrial electron transport, and with a variety of exogenous antioxidants (5, 6).

Antioxidants also inhibit the activation of nuclear factor-KB and specificity factor 1, and inhibit the increase in monocyte chemoattractant protein-1 or PAI-1 seen with hyperglycemia, Ang II, AGE as well as thromboxane A2 (7).

Through enhanced production of ROS, transition from renal tubular epithelial cells to mesenchymal cells has been demonstrated (8). This process leads to interstitial fibrosis. In endothelial cells, mitochondrial ROS increases as a response to hyperglycemia. Superoxide suppresses GAPDH, activates PKC, and increases AGE formation, thus causing tissue damage.

Benfotiamine, which is a lipid-soluble derivatives of thiamine, has been shown to suppress the activation of PKC, hexosamine pathway, NF-KB and AGE formation (9) seen with hyperglycemia. It has also been shown to suppress retinopathy development in diabetic rats (9), but a similar effect on renal tissue has not been demonstrated so far.

Hemodynamic, functional and structural changes in diabetic nephropathy have been linked to alterations in NO signaling. (10)

Synthesis of both NO and superoxide is increased in diabetes (11), and this imbalance alters the hemodynamics in the
Oxidative stress is an important pathogenetic factor in the causation of diabetic nephropathy. Therapeutic strategies which reduce the burden of oxidative stress may be useful in managing this condition.

**References**


Author Information

Navneet Agrawal  
Dept of Medicine, GR Medical College, Gwalior, India

Sanjeev Kumar Singh  
Dept of Biochemistry, GR Medical College, Gwalior, India

Neelima Singh  
Dept of Biochemistry, GR Medical College, Gwalior, India

Sanjay Kalra  
B.R.I.D.E., Karnal, India

Gautam Srivastava  
B.R.I.D.E., Karnal, India