

# Oxidative stress in the pathogenesis of diabetic nephropathy

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## Abstract

Nephropathy is an important chronic microvascular complication of diabetes, which has multiple pathophysiologic mechanisms. This review discusses the various oxidative and gluco-oxidative reactions which lead to renal damage in people with diabetes.

## 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.

## REDOX 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- $\beta$  (TGF- $\beta$ ) 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- $\beta_1$  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

kidney.

Interaction of NO by superoxide leads to vasoconstriction, due to loss of its vasodilator action. Excess superoxide per se causes renal vasoconstriction (12) while its conversion to H<sub>2</sub>O<sub>2</sub> leads to vasodilation (13).

Because of these varied actions, the net effect may be different at different stages of the disease. In early diabetic nephropathy, glomerular hyperfiltration and renal vasodilation may occur because of increased NO bioavailability due to enhanced NO production by eNOS. (14)

Glomerular mesangial cells and extracellular matrix proteins proliferate in response to hyperglycemia, Ang II and other factors via NO. NO has an antiproliferative effect on this reaction, via PKC and TGF- $\beta$ . Antioxidants have therefore been used to increase NO suppression of mesangial cell growth and synthesis of extracellular matrix protein in hyperglycemia.

NO and superoxide react to form peroxynitrite, which alters protein structure and function, and cause cell injury. (15)

If superoxide concentrations are reduced, there is less peroxynitrite production, and this is renoprotective. (16)

### **THERAPEUTIC IMPLICATIONS**

Oxidative stress is an important pathogenetic factor in diabetic nephropathy. It stands to reason, therefore, that drugs which reduce oxidative stress may provide renoprotective.

This effect has been seen with angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs), both of which are used as antihypertensive and renoprotective/vasculoprotective agents.

Specific inhibitors of oxidative stress have also been tried in animals and humans. These include aminoguanidine, which inhibits AGE, and prevents albuminuria. (17) Soluble blockers of RAGE have also been shown to reduce renal damage. (18)

Antioxidants such as vitamin E and C, lipoic acid, and taurine have shown beneficial effects on renal function (1) in short term trials.

While none of the existing antioxidants has shown therapeutic promise over long term, animal studies with the SOD mimetic drug called tempol have shown beneficial results in

reversing systemic hypertension and reducing GFR. (19) Future studies on this class of molecules may lead to a breakthrough in the management of diabetic nephropathy with antioxidants.

### **CONCLUSION**

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.

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