



# Diabetes and Renal Cell Aging, A Review



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## Abstract

Different environmental and genetic factors contribute to the process of aging as the ultimate cause of structural and physiological changes in body organs. Diabetes, with an increasing prevalence worldwide, is a progressive metabolic disease contributing to the acceleration of the aging process. Both types of the disease, type-1 and type-2, affect the kidney with different degrees, including nephropathy, in which the kidney function changes may develop into hyperfiltration, albuminuria and ultimately end-stage renal disease (ESRD). Diabetes damages the kidney through different mechanisms of inflammation, oxidative stress and the basement membrane thickening, and will turn into ESRD or kidney failure if it is not properly managed. This review aimed to increase researcher focus on diabetes as a facilitating agent to kidney tissue and cells aging.

**Keywords:** Aging; Diabetes; Kidney; Oxidative stress

## Introduction

Aging is a complex process that develops through changes in molecular pathways and different biochemical events that change body organs [1]. Aging causes structural, physiological and also histological changes in the kidney, which develops into glomerulosclerosis and tubular atrophy [2,3]. The aging-associated vascular changes impair the renal blood flow, cause kidney damage [4], reduce the number and increase the size of glomeruli, which in turn cause glomerular structural changes [5]. The aging-associated functional changes that occur in the kidney generally involve glomeruli, tubules and the endocrine system [6]. Diabetes constitutes a cause of renal cell aging and the associated renal changes.

## Diabetes

Diabetes is a common disease with a growing prevalence rate in underdeveloped and developing countries, which has turned to a major health concern in human societies. Research suggests that the number of diabetics will reach 300 million by 2025. With 4 million diabetic deaths annually reported, diabetes is considered the cause of 9% of deaths across the world [7].

## Diabetes and Renal Aging

Glomerular hypertrophy in diabetic nephropathy is associated with thickened basement membrane. Diabetic nephropathy is

a diabetic disorder contributing to ESRD and is divided into four stages of glomerular basement membrane thickening, mesangial expansion, nodular sclerosis and advanced diabetic glomerulosclerosis [8].

## Mechanisms Contributing To Diabetic Nephropathy

### Transforming growth factor beta (TGF-β)

Hyperglycemia causes both cell destruction and the production of toxic products such as the profibrotic protein TGF-β [9], whose activity is increased in diabetics and causes the activity of other growth factors such as CTGF to increase [10], which ultimately causes the increased production of extracellular matrix in glomerular mesangium and decelerates the glomerular matrix removal through collagenase inhibition [9].

### Tumor necrosis factor alpha (TNF-α)

Inflammation and inflammatory factors such as TNF-α play a key role in diabetic nephropathy [11]. TNF-α is overexpressed in diabetics [12] and significantly damages the kidney by causing reduction of blood flow and filtration rate [13]. Nephron plays a key role in regulating the filtration function and its dysfunction causes proteinuria. TNF-α causes the overexpression of nephron in renal epithelial cells and podocytes, and ultimately leads to increased functional changes in the kidney [14].

## Advanced glycosylated end product (AGE)

In long-term hyperglycemia, glucose binds to amino acids of the blood or tissues and causes the production of AGEs and structural changes in proteins [9]. These products can function with or without their receptors, namely Receptor Advanced Glycosylated End Product (RAGE), which is crucial for biological mechanisms. RAGE is a receptor of the immunoglobulin superfamily, which is expressed in cells, including macrophages, endothelial cells, mesangial cells and podocytes in the kidney. AGEs and RAGE binding stimulates the protein kinase C (PKC), which plays a key role in the proliferation and differentiation of cells and in the increased extracellular matrix, all of which cause the glomerular basement membrane thickening, increased glomerular permeability and over expression of Nuclear Factor-kappa B (NF- $\kappa$ B), TGF- $\beta$  and Vascular Endothelial Growth Factor (VEGF), which in turn cause the progression of diabetic nephropathy [15,16].

## NADPH Oxidase

Hyperglycemia causes the over expression of NADPH oxidase in mesangial cells through the PKC pathway [17,18]. Increased levels of NADPH oxidase elevate oxidative stress in mesangial cells and tubular endothelial cells [19,20]. Moreover, oxidative stress induced by NADPH oxidase causes mesangial expansion and albuminuria via the over expression of fibronectin and Collagen I [21].

## Endothelin 1 (ET-1)

The vasoconstrictor polypeptide ET-1 is produced in the vascular endothelium [22] and has two receptors including ETA and ETB [23]. This factor contributes to diabetic nephropathy, cardiovascular diseases such as hypertension and increased NADPH as the inducer of ROS in renal cells. In diabetes mellitus, the over expression of ET-1 in glomeruli and endothelial cells causes diabetic nephropathy [24], activation of ETA, production of TGF- $\beta$  and therefore inflammation [25,26].

## Urotensin II

Urotensin II is an 11 amino acid peptide with vasoconstrictive and profibrotic effects that binds to G protein-coupled receptor-14 (GPR-14). Diabetes and diabetic nephropathy are associated with increased levels of this factor, which contributes to vascular endothelial dysfunction. Urotensin II also increases both NADPH oxidase activities and mediates reactive oxygen species (ROS) generation [27,28].

## Cannabinoid receptor (CB)

There are two types of G-protein coupled CBs in mesangial cells, namely CB1 and CB2 [29]. Increased levels of CB1 in renal damage cause kidney hypertrophy and glomerular disease which is associated with proteinuria and elevated plasma creatinine [30]. A review of literature suggests that CB1 inhibition helps ameliorate albuminuria by preventing the downregulation

of neopterin levels and product number in mouse kidney [31]. CB2 activation plays a key role in managing diabetic nephropathy. Research suggests lower expression levels of glomerular CB2 in diabetic nephropathy as well as albuminuria reduction by agonists in diabetes-induced nephropathy in mice [32].

## Beta-galactosidase as a marker of senescent cells

Beta-galactosidase is a eukaryotic lysosomal hydrolase that isolates  $\beta$ -d-galactosidase from  $\beta$ -d-galactosidase and its activity is maximized at pH 3-5. Senescence-associated beta-galactosidase (SA- $\beta$ -Gal) is a special type of beta-galactosidase which was first observed in senescent cells in 1995 and is widely used in studies of cellular aging. Moreover, the optimal activity of this marker is at pH 6 [33]. The main advantage of this enzyme compared to other markers is its simplicity of measurement and detection and its capacity for in situ identification of senescent cells in their heterogeneous cell populations [34].

No specific mechanisms have been identified for the increased number of SA- $\beta$ -Gal-positive cells during aging and different factors can contribute to triggering its activity at pH 6, including differences in position, frequency and cycle of splicing mechanisms [35]. This enzyme can therefore be used as a marker to evaluate renal cell aging caused by diabetes.

## Conclusion

The present study proposed diabetes as a factor contributing to the acceleration of the renal cell aging process. Diabetes was found to affect renal cell aging through pathways of TGF- $\beta$ , TNF- $\alpha$ , AGEs, NADPH oxidase, ET-1, Urotensin II and CBs. Diabetic nephropathy and ultimately the kidney failure is inevitable unless diabetes is properly managed. SA- $\beta$ -Gal is also recommended to be used as a marker to evaluate the diabetes-associated aging level of renal cells.

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