Diabetes Mellitus (DM) is a group of metabolic diseases associated with increased oxidative stress due to elevated glucose levels in the plasma. DM patients suffer from greater incidence of microvascular complications such as retinopathy and nephropathy (DN). DN is the leading cause of End Stage Renal Disease (ESRD) and accounts for approximately 40% of all patients who require kidney transplantation [1]. The well-known risk factors for DN are uncontrolled DM and genetic factors. Reactive oxygen species, particularly those derived from iron, have been implicated in the progression of DN. Hence, the antioxidant protein Haptoglobin plays a central role in the development of DN.

Hp is an acute phase protein that acts as an antioxidant by virtue of its ability to bind free hemoglobin (Hb) and prevent heme-iron–mediated oxidation accompanied by tissue damage. Whenever Hb is released into the circulation, it binds immediately to Hp to form an Hp-Hb complex that is rapidly removed, predominately by the macrophage CD163 scavenger receptor expressed on Kupffer cells in the liver. Two classes of Hp alleles are known [1,2]. While the Hp 1 allele is found in all animal species, the Hp 2 allele is present only in humans, with homozygous (1-1 or 2-2) and heterozygous (2-1) possible genotypes. Several studies have revealed profound differences in the antioxidant capacity of the Hp proteins. The Hp1 protein is superior to the Hp2 protein in binding to free Hb and neutralizing its oxidative potential. Moreover, Hp 2-2 is associated with greater incidence of cardiovascular disease. Previously our group generated a genetically engineered mouse that expresses the Hp 2-2 genotype in an Hp knockout background. This mouse represents DN with the spectrum of micro- and macro-vascular complications similar to the human disease. Using this mouse model we have demonstrated marked differences in renal structure and function between the Hp 1-1 and Hp 2-2 DM mice; Hp 2-2 DM mice had increased features of glomerular disease characteristic of early human DN including a significant increase of iron deposits in the lysosomes of the proximal tubule cells (PCT).

Lino et al demonstrated that desferrioxamine suppressed the enhanced glomerular O2– production with subsequent decrease in PGE2 production. Antioxidant therapy may be beneficial in preventing the development of diabetic nephropathy [2]. We have demonstrated that vitamin E provided significant protection against the development of functional and histological features characteristic of DN to Hp 2-2 DM mice; Hp 2-2 DM mice had increased features of glomerular disease characteristic of early human DN including a significant increase of iron deposits in the lysosomes of the proximal tubule cells (PCT).

A further protein that was recently defined as an antioxidant is the anti-aging Klotho protein. The Klotho gene is expressed predominantly in the proximal and distal tubules of the kidney. It encodes a single pass trans-membrane protein that functions as a co-receptor for FGF-23, a bone-derived hormone that suppresses phosphate re-absorption and vitamin D biosynthesis in the kidney. The extracellular domain of Klotho is shed and secreted, and functions as a humoral factor with pleiotropic activities, including suppression of oxidative stress. Previous studies have indicated that renal Klotho gene expression is regulated by Pathophysiological conditions including long-term hypertension, DM, and chronic renal failure in the rat models. Furthermore, renal Klotho expression is severely reduced in the convoluted tubule cells of chronic kidney disease (CKD) both in mice and in humans [4].

It is not known if exogenous klotho attenuates diabetic nephropathy (DN). Exogenous klotho attenuated HG-induced TGF-β bioactivity, type II TGF-β receptor (TGF-βRII) protein expression
Podocytes exhibit active autophagy process under normal glucose stress via free radicals in PCT cells, and in podocytes. Actived under high glucose conditions, with increased oxidative stress, with the pathogenesis of DN. Autophagy pathway in the kidney is important in these patients. Recently a review by Mary Choi and her group showed that administration of active vitamin D may be determinent. Additionally, there is some evidence that Vitamin D analogs supplementation (as calcitriol or paricalcitol) improves the condition of kidneys of CKD patients and their survival [7].

DN includes PCT injury and active vitamin D deficiency, but the precise mechanism behind it needs to be determined. Our DN patients with different Hp genotypes, as well as our genetically engineered Hp 2-2 DN mouse model, enable us to explore why progression to end-stage renal disease is increased in DM individuals with the Hp 2-2 genotype and show that administration of active vitamin D may be important in these patients.

Autophagy is a highly regulated lysosomal protein degradation pathway that removes protein aggregates and damaged or excess organelles in order to maintain intracellular homeostasis and cell integrity. Recently a review by Mary Choi and her group showed that the accumulation of damaged proteins and organelles is associated with the pathogenesis of DN. Autophagy pathway in the kidney is activated under high glucose conditions, with increased oxidative stress via free radicals in PCT cells, and in podocytes.

The autophagy-lysosomal degradation pathway is likely to play an essential role in maintaining podocyte function and integrity. Podocytes exhibit active autophagy process under normal glucose levels, suggesting that podocytes require a high basal level of autophagy to maintain podocytes and glomerular maintenance. Furthermore, it is interesting that the loss of autophagy in podocytes affects the ultrastructure and function of these cells but also that of nearby mesangial cells, which become sclerotic. New evidence suggests that targeting the autophagic pathway to activate and restore autophagy activity may be Reno-protective in diabetic patients, especially via the mTORC1 [8].

Thet new anti-diabetic drugs such as, Dapagliflozin and others contain a potent selective reversible inhibitor of SGLT2, expressed exclusively in the proximal tubule of the kidney. Between the new anti diabetic medications that target a specific pathophyslogic pathway, the SGLT2 inhibitors and Metformin are of major interest in the future, in the treatment of early stage DN [9].

References