Kidneys are two bean-shaped internal organs in which are on the left and right sides of the back of the abdomen (Fig. 1). The main functions of kidneys are to (1) excrete waste matter from the body as urine, (2) reabsorb electrolytes necessary for the body and maintain healthy concentrations of electrolytes, (3) release an enzyme called rennin to adjust blood pressure by controlling vascular-constriction substance (angiotensin II), (4) secrete erythropoietin for the formation of red cells in bone marrow and (5) convert vitamin D to active-type vitamin D3 (cholecalciferol) to precipitate calcium in bone.

When renal function decreases, waste and excess water accumulate in the body, swelling appears, the balance of electrolytes is disturbed, blood pressure increases, anemia occurs, bones become brittle and a variety of other symptom appear. Kidney diseases include various disorders such as chronic glomerulonephritis, diabetic nephropathy, renal sclerosis, polycystic kidney disease and various other symptom appear. Kidney diseases include various disorders such as chronic glomerulonephritis, diabetic nephropathy, renal sclerosis, polycystic kidney disease and various other symptom appear. Kidney diseases include various disorders such as chronic glomerulonephritis, diabetic nephropathy, renal sclerosis, polycystic kidney disease and various other symptom appear. Kidney diseases include various disorders such as chronic glomerulonephritis, diabetic nephropathy, renal sclerosis, polycystic kidney disease and various other symptom appear.

The main functions of kidneys are the excretion of urine out of the body as waste, maintenance of electrolytes, and the regulation of blood pressure. Therefore, a declining in kidney function leads to various biological malfunctions. The number of kidney dialysis patients in Japan is beyond 300,000. Its primary cause is diabetic nephropathy, and the cause of diabetic nephropathy is the persistent hyperglycemic condition. A hyperglycemic state leads to an activity increase of protein kinase C (PKC) and increases in glycative stress and oxidative stress. It also increases the accumulation of advanced glycation end products (AGEs) and it brings about physiological structural changes in the kidney. Therefore, there is a focus on glycative stress as the cause of the development of nephropathy. Although several AGE formation inhibitors have been developed to date, they have not been used for clinical purpose due to their strong side effects. Meanwhile, the positive effects of thiamine and pyridoxamine, types of vitamins, on the kidney functions of diabetic patients has been reported. Renal function improving effects have also been recognized in the research using receptors for AGE (RAGE) deficient mice. Furthermore, in research using mice with progressed glyoxalase 1 (GLO1) activity, glycative stress and kidney aging are alleviated. The development of new drugs based on RAGE and GLO1 are expected for the treatment of the kidney.

The number of kidney dialysis patients in Japan was greater than 300,000 at the end of 2013. The average number of kidney dialysis patients increased by approximately 6,000 a year during the 10 years before 2013. Therefore, it is no exaggeration to say that kidney disease is a national disease in Japan. The initial cause of disease in new patients introduced into dialysis in 2013 was diabetic nephropathy (43.8%), the second was chronic glomerulonephritis (18.8%) and the third was nephrosclerosis (13.1%). Since 1998, diabetic nephropathy has replaced chronic glomerulonephritis as the most common disease for dialysis patients in Japan. Because the number of diabetic nephropathy cases is increasing, there has been a focus on glycative stress as a cause of its development.

The onset of diabetic nephropathy starts with the continuous presence of microalbuminuria (20 ~ 200 μg/min). If the microalbuminuria condition is left untreated, as a condition from the stage of “Mibyo (not yet ill)” of chronic renal failure to its terminal stage, and it has now been recognized as a diagnostic indicator for diminished renal function.

The number of kidney dialysis patients in Japan was greater than 300,000 at the end of 2013. The average number of kidney dialysis patients increased by approximately 6,000 a year during the 10 years before 2013. Therefore, it is no exaggeration to say that kidney disease is a national disease in Japan. The initial cause of disease in new patients introduced into dialysis in 2013 was diabetic nephropathy (43.8%), the second was chronic glomerulonephritis (18.8%) and the third was nephrosclerosis (13.1%). Since 1998, diabetic nephropathy has replaced chronic glomerulonephritis as the most common disease for dialysis patients in Japan. Because the number of diabetic nephropathy cases is increasing, there has been a focus on glycative stress as a cause of its development.

The onset of diabetic nephropathy starts with the continuous presence of microalbuminuria (20 ~ 200 μg/min). If the microalbuminuria condition is left untreated,
80% of patients with type 1 diabetes would develop overt albuminuria (>200 μg/min) within 15 years and 50% of them would progress to end-stage kidney disease (ESKD) within 10 years. In the case of patients with type 2 diabetes, 20-40% of them would develop overt albuminuria and 20% of them would move to ESKD in the 20 years after that.

2. AGE excretion in kidneys

Kidneys play an important role in the excretion and inhibition of accumulation of AGEs. Membrane receptors called megalin exist in proximal convoluted tubules and reabsorb low molecular protein filtrated from urine. AGEs in blood, which were formed in vivo, are collected in renal tubular cells by endocytosis, after combining with megalin in kidneys. However, if a large amount of AGEs are taken up in megalin, the decomposition of AGEs in lysosomes is saturated. As a result, AGEs accumulate in renal tubular cells.

Kidneys are involved in metabolism and excretion of AGEs orally taken into the body. In an experiment where rats were intravenously dosed with pentosidine, 35% of the pentosidine accumulated in the kidneys. Furthermore, it was reported that the AGE concentration in the urine of the healthy people who took in low-AGE food was reduced.

3. AGEs and diabetic nephropathy

As recognized histological features of diabetic nephropathy, there is a thickening of the glomerular basement membrane and an increase in the mesangial matrix. The accumulations of AGEs are observed in various parts such as glomerular basement membrane, mesangial matrix, podocyte, renal tubular cells and endothelial cells (Fig. 2). Ultimately, it results in renal failure accompanied with glomerular sclerosis.

The cause of diabetic nephropathy is a continual hyperglycemic state. Therefore, complicated causes are involved in the process from the onset of diabetic nephropathy to renal failure. Glomerular hyperfiltration and glomerular hypertension are the greatest changes that occur in glomerulus at an early stage of the onset of diabetes. Glomerular hyperfiltration and increased intraglomerular pressure injures endothelial cells and cause macrophage infiltration and platelet aggregation. Cytokine and other substances released from these cells accelerate the production of extracellular matrix from mesangial cells and accelerates the progression of glomerular sclerosis. Furthermore, the extensive stimulation of mesangial cells accelerates the production of extracellular matrix. The increase of the activity of protein kinase C (PKC) caused by the increase of intracellular diacylglycerol caused by hyperglycemic state and the accumulation of AGEs formed by glycative stress and oxidative stress, become important progression factors of neuropathy (Fig. 3).

The atrophy of proximal convoluted tubules and the fibrosis of tubulointerstitium also progress. Metabolic disorder, blood flow change, expressions of cytokine and transforming growth factor-β (TGF-β) are involved in these histological changes.
4. Response to the treatment of diabetic nephropathy as measures against glycative stress

The actions to inhibit urine proteins and the histological changes in the kidney are recognized in AGEs formation inhibitors such as aminoguanidine, thiazolidine derivatives, and OPB-9195 [(+/-)2-isopropylidenehydrazono-4-oxothiazolidin-5-ylcarboxanilide]. However, these drugs are known to have strong side effects, so it is difficult to use these drugs for clinical applications. On the other hand, renal function improvement effects for diabetic patients are recognized in thiamine (vitamin B1) and pyridoxamine (vitamin B6 analog compound). In research using RAGE deficient mice exhibiting the characteristics of progressive glomerular sclerosis and decreased renal function, the improvement of renal function was recognized. The result of this research suggests that it is possible that RAGE is involved in the onset of diabetic nephropathy and RAGE becomes the target of treatment. In a research where the activity of glyoxalase I (GLO1), a kind of dicarbonyl compound eliminating enzyme, was accelerated, oxidative stress and kidney aging were alleviated. Therefore, the development of new drugs based on GLO1 is expected for the treatment of kidney disorders.

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Conflict of interest statement

There are no items deemed to be conflicts of interest in this research.

Reference