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Recent evidence in the etiology and treatment for diabetic kidney disease

Diabetic kidney disease (DKD) is a microvascular complication of diabetes and the leading cause of end-stage renal disease (ESRD) in many countries. Recently, accumulated evidence has provided new insights into the etiology and treatment for DKD.

Albuminuria and decline of estimated glomerular filtration rate (eGFR) are characteristic features of DKD, and a risk factor for progression to ESRD and cardiovascular diseases (CVD). Baseline data of Japan Diabetes Complication and its A prevention prospective study showed that the prevalence of albuminuria is approximately 30% in Japanese patients with type 2 diabetes[1]. This value is lower compared with the data of previous studies, suggesting that the prevalence of albuminuria has recently been decreasing. Yokoyama *et al.*[2] analyzed the prognosis of DKD without albuminuria (non-albuminuric DKD) in their follow-up study (JDDM54). They divided Japanese patients with type 2 diabetes into four DKD phenotypes on the basis of albuminuria (>30 mg/g creatinine) and reduced eGFR (<60 mL/min/1.73 m^2) at baseline: (i) no-DKD; (ii) albuminuric DKD without reduced eGFR; (iii) non-albuminuric DKD with reduced eGFR; and (iv) albuminuric DKD with reduced eGFR. As a result, in non-albuminuric DKD, the risks of death or CVD were not higher than those with the no-DKD phenotype, and the annual decline in eGFR was slower than in other DKD phenotypes during the mean follow-up period of 9.7 years. They conclude that non-albuminuric DKD did not have a higher risk of death, CVD or renal function decline than the other DKD phenotypes. It is important to measure albuminuria for early diagnosis of DKD, and prevention of ESRD and CVD in patients with diabetes.

Hypertension and dyslipidemia are involved in the etiology of DKD, in addition to hyperglycemia[3–5]. As for the treatment of dyslipidemia, lowering of low-density lipoprotein cholesterol by statin has been shown to reduce the risk of ESRD in type 2 diabetes patients with overt proteinuria[4]. Various mechanisms are believed to be involved in the pathogenesis of DKD, including genetic factors, activation of polyol pathway and protein kinase C, glomerular hypertension and hyperfiltration, accumulation of advanced glycation end-products, oxidative stress, overexpression of transforming growth factor-β, and the inflammatory process (microinflammation)[6]. These mechanisms are potential candidates for the therapeutic target of DKD (Figure 1). Recently, it has been reported that inflammasomes are implicated in the pathogenesis of renal inflammation in DKD[7]. Pattern recognition receptors, including nucleotide-binding oligomerization domain-like receptors, recognize exogeneous and endogenous ligands to stimulate inflammasome assembly followed by caspase-1 activation, and secretion of interleukin-1β and interleukin-18. We previously found that serum and urinary levels of interleukin-18 are elevated and positively corelated with albuminuria in patients with type 2 diabetes, suggesting that inflammasome plays a role in the pathogenesis of DKD[6]. Tumor necrosis factor is one of the major inflammatory cytokines. Gohda *et al*[8]. reported that increased concentrations of serum tumor necrosis factor receptors are positively associated with albuminuria, and negatively associated with the eGFR in patients with type 2 diabetes. They suggest that an increase in serum tumor necrosis factor receptors might result from their increased systemic production in the recent article.

There has been accumulating evidence of renoprotective effects of sodium–glucose cotransporter 2 (SGLT2) inhibitors in patients with type 2 diabetes by cardiovascular outcome trials, including the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients-Removing Excess Glucose (EMPA-REG OUTCOME) trial, Canagliflozin Cardiovascular Assessment Study (CANVAS) program and Dapagliflozin Effect on Cardiovascular Events – Thrombolysis in Myocardial Infarction 58 (DECLAER-TIMI 58). These trials strongly suggest the renoprotective effects of SGLT2 inhibitor in patients with type 2 diabetes[9]. Kadowaki *et al.*[10] reported that empagliflozin reduces the risk of development or progression of DKD in Asian patients with type 2 diabetes. Furthermore, Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) showed that canagliflozin reduced the risk of primary renal outcome consisting of ESRD, doubling of serum creatinine and death from renal or CVD in patients with type 2 diabetes with overt poteinuria[11]. There have been several postulated mechanisms of renoprotective actions of SGLT2 inhibitors, including the improvement of the impaired tubuloglomerular feedback system, in addition to the improvement of metabolic abnormalities[9]. In an animal experiment, Kimura *et al.*[12] showed that canagliflozin reduced oxidative stress in diabetic rats.

Glucagon-like peptide-1 (GLP-1) is an incretin hormone that enhances insulin secretion from pancreatic β-cells. Recent studies have shown that GLP-1 receptor is expressed not only in the pancreas, but also in many organs. GLP-1 has been shown to exert anti-inflammatory effects in *in vitro* and *in vivo* studies. We previously showed *in vitro* that exenatide exerts an anti-inflammatory effect by

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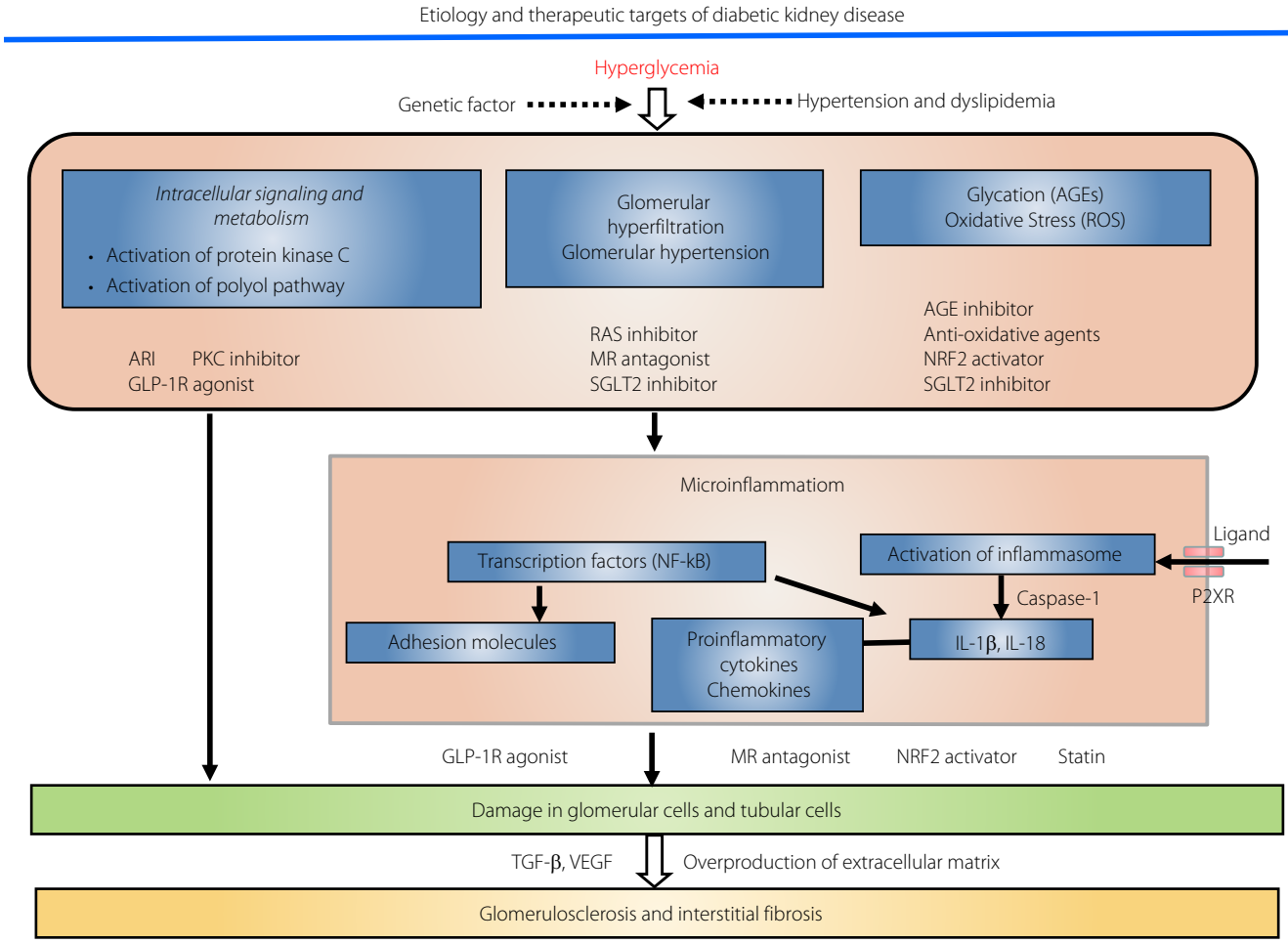

Figure 1 | Etiology and therapeutic targets of diabetic kidney disease (DKD). Hyperglycemia induces diabetic nephropathy through various mechanisms, including activation of the polyol pathway and protein kinase C (PKC), glomerular hypertension and hyperfiltration, glycation, oxidative stress, and the inflammatory process. These pathways are therapeutic targets of nephropathy. In addition to renin–angiotensin system (RAS) inhibitor, aldose reductase inhibitor (ARI), PKC inhibitor, advanced glycation end-product (AGE) inhibitor, mineralocorticoid receptor (MR) antagonist and nuclear factor erythroid 2-related factor 2 (NRF2) activator are potential therapeutic drugs, and sodium–glucose cotransporter 2 (SGLT2) inhibitor and glucagon-like peptide-1 (GLP-1R) agonist have been shown to be effective for DKD. IL-1β, interleukin-1β; NF-κB, nuclear factor-kB; P2XR, purinergic P2X receptors; TGF-β, transformation growth factor-β; VEGF, vascular endothelial growth factor.

decreasing the expression of intercellular cell adhesion molecule-1 in glomerular endothelial cells. Furthermore, exendin-4 – a GLP-1 receptor agonist – ameliorated albuminuria, glomerular hyperfiltration, glomerular hypertrophy, and mesangial matrix expansion in type 1 diabetic rats with anti-inflammatory and anti-oxidative effects[13]. Weiqin *et al.*[14] reported that protein kinase C and protein kinase A are involved in renoprotective effects of GLP-1 from their animal experiments. In clinical trials, liraglutide and semaglutide have shown renoprotective effects in patients with type 2 diabetes. In the Liraglutide Effect and Action In Diabetes: Evaluation of Cardiovascular Outcome Risks (LEADER) trial[15], administration of liraglutide significantly suppressed the nephropathy-related outcomes (onset of macroalbuminuria, doubling of the serum creatinine level and eGFR ≤45 mL/min/1.73 m^2, need for continuous renal replacement therapy or death from renal disease).

Growing evidence has provided new insights and future direction for the etiology and treatment of DKD. This evidence might accelerate the development of new drugs for DKD, and GLP-1 receptor agonist and SGLT2 inhibitor would improve the prognosis of DKD.

DISCLOSURE

The author declares no conflict of interest.

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REFERENCES

1. Shikata K, Kodera R, Utsunomiya K, *et al*. Prevalence of albuminuria and renal dysfunction, and related clinical factors in Japanese patients with diabetes: the Japan Diabetes Complication and its Prevention prospective study 5. *J Diabetes Investig* 2020; 11: 325–332.
2. Yokoyama H, Araki S, Kawai K, *et al*. The prognosis of patients with type 2 diabetes and nonalbuminuric diabetic kidney disease is not always poor: implication of the effects of coexisting macrovascular complications (JDDM 54). *Diabetes Care* 2020; 43: 1102–1110.
3. Okamura T, Ushigome E, Kitagawa N, *et al*. Maximum morning home systolic blood pressure is an indicator of the development of diabetic nephropathy: the KAMOGAWA-HBP study. *J Diabetes Investig* 2019; 10: 1543–1549.
4. Shikata K, Haneda M, Ninomiya T, *et al*. Randomized trial of an intensified, multifactorial intervention in patients with advanced-stage diabetic kidney disease: Diabetic Nephropathy Remission and Regression Team Trial in Japan (DNETT-Japan). *J Diabetes Investig* 2021; 12: 207–216.
5. Song KH, Jeong JS, Kim MK, *et al*. Discordance in risk factors for the progression of diabetic retinopathy and diabetic nephropathy in patients with type 2 diabetes mellitus. *J Diabetes Investig* 2019; 10: 745–752.
6. Shikata K, Makino H. Microinflammation in the pathogenesis of diabetic nephropathy. *J Diabetes Investig* 2013; 4: 142–149.
7. Tang SCW, Yiu WH. Innate immunity in diabetic kidney disease. *Nat Rev Nephrol* 2020; 16: 206–222. 380: 2295–2306.
8. Gohda T, Kamei N, Kubota M, *et al*. Fractional excretion of tumor necrosis factor receptor 1 and 2 in patients with type 2 diabetes and normal renal function. *J Diabetes Investig* 2021; 12: 382–389.
9. Koya D. Diabetic kidney disease: its current trends and future therapeutic perspectives. *J Diabetes Investig* 2019; 10: 1174–1176.
10. Kadowaki T, Nangaku M, Hantel S, *et al*. Empagliflozin and kidney outcomes in Asian patients with type 2 diabetes and established cardiovascular disease: results from the EMPA-REG OUTCOME® trial. *J Diabetes Investig* 2019; 10: 760–770.
11. Perkovic V, Jardine MJ, Neal B, *et al*. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med* 2019; 380: 2295–2306.
12. Kimura Y, Kuno A, Tanno M, *et al*. Canagliflozin, a sodium-glucose cotransporter 2 inhibitor, normalizes renal susceptibility to type 1 cardiorenal syndrome through reduction of renal oxidative stress in diabetic rats. *J Diabetes Investig* 2019; 10: 933–946.
13. Kodera R, Shikata K, Kataoka HU, *et al*. Glucagon-like peptide-1 receptor agonist ameliorates renal injury through its anti-inflammatory action without lowering blood glucose level in a rat model of type 1 diabetes. *Diabetologia* 2011; 54: 965–978.
14. Yin W, Jiang Y, Shiqing X, *et al*. Protein kinase C and protein kinase A are involved in the protection of recombinant human glucagon-like peptide-1 on glomeruli and tubules in diabetic rats. *J Diabetes Investig* 2019; 10: 613–625.
15. Mann JFE, Ørsted DD, Brown-Frandsen K, *et al*. Liraglutide and renal outcomes in type 2 diabetes. *N Engl J Med* 2017; 377: 839–848.

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