Medical Research Archives

ESMED
European Society of Medicine

OPEN ACCESS

Published: February 28, 2023

Citation: Zhang X and Leehey D, et al., 2023. Inflammation in Diabetic Kidney Disease: Focus on New Therapeutic Considerations, Medical Research Archives, [online] 11(2). https://doi.org/10.18103/mra.v11i2.3614

DOI
https://doi.org/10.18103/mra.v11i2.3614

ISSN: 2375-1924

RESEARCH ARTICLE

Inflammation in Diabetic Kidney Disease: Focus on New Therapeutic Considerations

Xin Zhang, M.D; David Leehey, M.D.

Division of Nephrology, Department of Medicine
Loyola University Medical Center, Maywood, IL and Hines VA Hospital, Hines IL

Correspondence:
D. Leehey 111L, Hines VA Hospital, Hines IL 60141
Phone: (708)2022589
Email: david.leehey@va.gov

The authors have no conflicts of interest to declare.

ABSTRACT
Diabetic kidney disease (DKD) is the most common cause of end-stage renal disease (ESRD) in the U.S. and worldwide. A role of chronic low-grade inflammation in the microvascular complications in diabetic patients has now been widely accepted, and anti-inflammatory therapies for DKD are being actively pursued. Such therapies may be especially useful in the treatment of patients with chronic kidney disease (CKD) with normal to only moderately increased albuminuria, a DKD phenotype which is becoming more frequent. Current pharmacologic treatment for DKD includes inhibitors of the renin-angiotensin-aldosterone system (RAAS) and the sodium-glucose co-transporter 2 (SGLT2) in the proximal tubule. Both classes of agents are known to reduce blood pressure but also are thought to have anti-inflammatory, antioxidant, and anti-fibrotic effects independent of their hemodynamic actions. Large clinical trials with experimental agents such as bardoxolone and selonsertib that target inflammation and oxidative stress in DKD have been carried out or are in progress. The non-specific phosphodiesterase inhibitor pentoxifylline (PTX) is also being studied in a large US trial to see if this FDA-approved drug may be able to be repurposed to treat DKD. Other agents have also shown promising effects in small clinical trials but require further large-scale investigation.

Keywords: diabetes, chronic kidney disease, diabetic kidney disease, inflammation, therapy

Introduction

Diabetic kidney disease (DKD), one of the most important microvascular complications of diabetic mellitus (DM), is the predominant cause of end-stage renal disease (ESRD) worldwide[1,2]. The pathogenesis of DKD includes mesangial expansion, endothelial dysfunction, loss of glomerular podocytes, and interstitial fibrosis. The classic natural history of DKD is the development of albuminuria followed by deterioration in kidney function, eventually leading to ESRD. The characteristic renal pathologic findings are diffuse and nodular glomerulosclerosis[3]. Proteinuria is an important predictor of outcome in chronic kidney disease (CKD), including DKD[3,4]. Risk factors for progression to ESRD in patients with DKD include hyperglycemia, hypertension, severity of albuminuria, and presence of retinopathy[5]. High salt intake and arteriosclerosis are implicated in the development of DKD, especially in type 2 DM patients[6]. Patients with DKD are at markedly increased risk for cardiovascular events and mortality[7,8].

DKD has been traditionally considered to be caused by the adverse effects of hyperglycemia (metabolic theory) and hemodynamic alterations which increase systemic and intraglomerular pressure (hemodynamic theory) in genetically predisposed patients. Nearly three decades ago, Hagesawa et al. initially suggested based on studies in diabetic animals that proinflammatory cytokines might also be involved in the pathogenesis of DKD[9]. The sources of cytokine production by the kidneys in DM are both infiltrating macrophages and resident kidney cells. Hyperglycemia-induced production of reactive oxygen species (ROS), pro-inflammatory factors, and growth factors such as transforming growth factor-beta (TGF-β) can induce renal damage, and a causal role for macrophages in the progression of DKD has been suggested in both rodents[10] and humans[11]. Various types of renal cells (endothelial, mesangial, epithelial, and tubular cells) are capable of synthesizing proinflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin 1 (IL-1), and interleukin 6 (IL-6). These cytokines, acting in a paracrine or autocrine manner, contribute to the pathophysiology of DKD[12]. Plasma concentrations of proinflammatory cytokines are elevated in patients with type 2 DM[13,14] and increase as nephropathy progresses[15,16]. Inflammation and oxidative stress are associated with both micro- and macro-vascular diabetic complications[17-19].

The pathways by which hyperglycemia induces low-grade inflammation are complex and still being elucidated. High glucose stimulates production of ROS in mesangial cells, which can be blocked by either angiotensin receptor blockers (ARBs) or NAD(P)H oxidase inhibitors, suggesting that oxidative stress in high glucose/diabetes may be due to stimulation of the angiotensin II-NAD(P)H oxidase system[20]. Angiotensin II is also known to stimulate TGF-β production, stimulating proinflammatory and profibrotic pathways in the kidneys, increasing production of cytokines such as TNF-α and interleukins[21]. In recent years, possibly due to better treatment of hyperglycemia and hypertension and the use of RAAS blockers, the prevalence of normal to only moderately increased albuminuric versus severely albuminuric DKD has increased. Less albuminuric DKD is thought to be predominately due to microvascular and tubulointerstitial injury mediated predominantly by inflammation[22]. Therefore, there has been growing interest in the development of anti-inflammatory agents for the treatment of DKD.

Targeting Inflammation in Diabetic Kidney Disease

A role of chronic low-grade inflammation in the microvascular complications in diabetic patients has now been widely accepted[23,24]. Several approaches have been proposed to treat inflammation in DKD, including lifestyle modifications (diet and exercise) and medications. Anti-inflammatory effects may explain some of the benefits of current pharmacologic management with RAAS blockers and SGLT2 inhibitors. Recent clinical trials with other anti-inflammatory therapies in DKD will also be reviewed.

- Renin-angiotensin-aldosterone system (RAAS) blockers

Numerous studies have shown that angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) slow the progression of DKD. In addition to their antihypertensive effects, which would be expected to primarily benefit glomerular disease, they also exert anti-inflammatory/antifibrotic actions mediated directly by RAAS inhibition[25-28]. This could result in improvement of interstitial and microvascular disease as well as glomerular disease. However, there are no large trials that have been performed with these agents in less albuminuric patients with DKD. In addition, there is concern that RAAS

blockers may actually increase susceptibility to acute kidney injury in patients who are non-albuminuric[22], possibly due to preventing constriction of the efferent arteriole.

- Sodium-glucose co-transporter 2 (SGLT2) inhibitors

In experimental models of type 1 and 2 DM, SGLT2 inhibitors have been shown to reduce oxidative stress, inflammatory mediators such as nuclear factor kappa B (NFκB), TNF-α, IL-6, monocyte chemoattractant protein-1 (MCP-1), macrophage infiltration, and fibrosis (fibronectin, TGF-β). They also upregulate anti-inflammatory and antifibrotic pathways[29-31]. In several animal models of DM, reduced glomerular and tubulointerstitial injury were observed following SGLT2 inhibition[30,32-35]. SGLT2 inhibition improves renal cortex hypoxia and thus decreases the deleterious effects of hypoxia such as oxidative stress, inflammation, apoptosis, and fibrosis in the kidney[36]. SGLT2 inhibitors stimulate ketogenesis; using ketone bodies as the source of energy alleviates inflammation and protects against tubular cell apoptosis and renal fibrosis[36].

Due to reduction in glomerular hypertension, SGLT2 inhibition reduces albuminuria[37,38]. In the EMPA-REG OUTCOME and CANVAS Program trials, SGLT2 inhibition also was shown to modestly attenuate increases in urine albumin excretion in patients with normoalbuminuria, suggesting the possibility of a long-term primary prevention effect[38,39]. Nevertheless, the risk of progressing from normo- to micro- or macroalbuminuria was not reduced in EMPA-REG OUTCOME[38]. Several large recent clinical trials (CREDENCE[40], DAPA-CKD[41], EMPA-KIDNEY[42]) have demonstrated marked cardiorenal protective effects of SGLT2 inhibitors. Although the CREDENCE and DAPA-CKD trials required patients to have albuminuria, in EMPA-KIDNEY, patients with an estimated glomerular filtration rate (eGFR) between 20 and 45 mL/min/1.73m^2 were enrolled regardless of the degree of albuminuria. A prespecified exploratory analysis of the annual rate of change in eGFR showed that empagliflozin slowed the rate of long-term eGFR decline among patients with a urinary albumin-to-creatinine ratio (UACR) of less than 300 mg/g at baseline (including patients with a UACR of <30)[42].

Since RAAS inhibition and SGLT2 inhibition are both renoprotective in DKD, there is much interest in the interactions between these two systems. Under hyperglycemic conditions, renin, the rate-limiting enzyme in the RAAS, is overexpressed in plasma and locally in cells, leading to increased angiotensin II production[43,44]. An increase in angiotensinogen production by elevated glucose may also be involved in increased local angiotensin II production in DM[45], which may contribute to inflammation[46]. SGLT2 inhibitors cause an initial transient plasma volume contraction leading to a compensatory, physiological and temporary activation of the systemic RAAS[47]. In contrast to the rise in RAAS markers in blood and urine, animal and human studies have demonstrated suppression of intrarenal RAAS activity with SGLT2 inhibition[48,49]. Treatment with SGLT2 inhibitors may decrease intrarenal angiotensinogen production[50], and suppression of the intrarenal RAAS may decrease oxidative stress and inflammation-related pathways at the tissue level[43,51,52].

- Pentoxifylline

Phosphodiesterases (PDEs) are a class of enzymes that hydrolyze cAMP and cyclic guanosine monophosphate and are involved in many physiologic processes including cell proliferation and differentiation, cell-cycle regulation, gene expression, cellular metabolism, apoptosis, and inflammation. PDEs are composed of 11 different families and each family contains different subtypes. Pentoxifylline (PTX) is a methylxanthine derivative with pleomorphic effects including nonspecific inhibition of PDEs. PTX was approved by the US Food and Drug Administration for the treatment of intermittent claudication and has been shown to have anti-inflammatory effects in both animal and human studies by inhibiting the production of proinflammatory cytokines[19,24].

Clinical data supporting a role for PTX in DKD have been accumulating for the past two decades. Most of the trials used a small number of subjects and were of short duration[53]. The PREDIAN trial[54], one of the larger studies performed to date, examined the renoprotective effects of PTX therapy in addition to RAAS blockade in 169 white patients with type 2 DM and stage 3 or 4 CKD and urinary albumin excretion of >30 mg/24 h. Treatment with PTX decreased proteinuria and urinary concentration of TNF-α and slowed decline in eGFR (2.1 vs 6.5 ml/min per 1.73 m^2) at the end of the study. However, the study was open-label, not placebo-controlled, and was not powered to detect differences in hard outcomes such as ESRD and mortality. The Cochrane group and several other meta-analyses concluded that although there is

evidence for some renoprotective effects of PTX, data are insufficient to guide therapy given that most included studies were poorly reported, small, and methodologically flawed[55-57]. The ongoing large-scale, multicenter PTXRx study (NCT03625648) is being conducted to determine whether this agent can reduce hard endpoints such as ESRD and death[53].

- Finerenone

There is growing evidence that pathophysiological overactivation of the mineralocorticoid receptor leads to inflammation and fibrosis and is a key driver of the progression of CKD and its associated morbidity and mortality. Both steroidal mineralocorticoid receptor antagonists (MRAs) as well as novel nonsteroidal MRAs can be used to inhibit mineralocorticoid receptor overactivation and reduce its deleterious effects by reducing proinflammatory and profibrotic gene expression[58,59]. The steroidal MRAs spironolactone and eplerenone have both demonstrated reduction in cardiovascular morbidity and mortality in patients with chronic heart failure and reduced left ventricular ejection fraction[60]. However, this benefit was not observed in patients with diabetes[61]. Importantly, their use is often associated with hyperkalemia, with the risk increased in diabetes and CKD. Small trials of steroidal MRAs added to either an ACE inhibitor or an ARB in DKD have been also associated with unacceptably high rates of hyperkalemia[62].

In contrast, finerenone has a nonsteroidal structure that allows it to bind to the mineralocorticoid receptor with a unique mechanism to inhibit recruitment of transcriptional cofactors involved in the expression of proinflammatory and profibrotic genes[63,64]. In animal models, finerenone reduced expression of proinflammatory and profibrotic markers and inhibited macrophage infiltration in the kidney, resulting in an improvement in proteinuria[65,66]. The ARTS-DN Phase IIb study of 823 patients with type 2 DM and albuminuria [UACR ≥30 mg/g] on stable therapy with an ACE inhibitor or ARB evaluated the safety and efficacy of different once-daily doses of finerenone compared with placebo[67]. Finerenone demonstrated a dose-dependent reduction in UACR (the primary outcome) of 25–38% compared with placebo over 90 days, while minimal adverse effects on potassium and renal function were observed. Interestingly, the effect of finerenone on albuminuria was independent of measured hemodynamic effects including blood pressure. The large FIDELIO-DKD trial[68] confirmed UACR improvement with finerenone in patients with DKD and more importantly demonstrated an 18% reduction in the composite kidney outcome. An analysis from the FIGARO-DKD study has also shown that among patients with DKD who were on a background of maximal RAS blockade therapy, finerenone led to a 36% relative risk reduction for ESRD[69]. Finally, a prespecified pooled analysis of FIDELIO-DKD and FIGARO-DKD (FIDELITY) reported a 23% reduction of the composite kidney outcome[70].

- Experimental Agents

A number of novel anti-inflammatory agents have been or are being studied in clinical trials of DKD.

  - Bardoxolone, a nuclear factor (erythroid-derived 2)-related factor 2 (Nrf2) activator, has been extensively studied in DKD. It is known that oxidative stress and inflammation are associated with impaired activity of the Nrf2 transcription factor, and activation of this pathway was shown to improve eGFR in DKD[71]. However, a large-scale clinical trial of bardoxolone in patients with DM and CKD stage 4 (BEACON) was halted due to excess adverse cardiovascular events[72,73]. A recent Japanese phase 2 trial demonstrated that measured GFR was increased by bardoxolone, but the drug was associated with peripheral edema[74].
  - Selonsertib, an inhibitor of apoptosis signal–regulating kinase 1 (ASK1), did not alter UACR in a phase 2 trial, but exploratory post hoc analyses suggested that it may slow CKD progression[75]. It is now being studied in the phase 3 MOSAIC trial (NCT04026165). Oxidative stress increases ASK1 activity, promoting inflammation, apoptosis, and fibrosis. ASK1 acts as an upstream regulator for the activation of p38 mitogen-activated protein kinase (MAPK) and c-Jun N-terminal kinase (c-JNK), two mediators of NF-KB activation and stimulation of inflammatory gene expression.
  - Propagermanium, an inhibitor of C-C chemokine receptor type 2 (CCR2) resulted in no change in UACR from baseline to 12 months in one study[76] while another unpublished study found a placebo-adjusted reduction in albuminuria from baseline (https://investors.dimerix.com/DownloadFile.axd?file=/Report/ComNews/20210128/02334227.pdf)

- CCX140 B, a selective CCR2 inhibitor, resulted in improvement in UACR at 52 weeks[77].
- Baricitinib, an inhibitor in inflammation caused by Janus kinases (JAK1/JAK2 inhibitor) resulted in improvement in UACR at week 24 in a phase 2 study[78].
- ASP8232, a novel inhibitor of vascular adhesion protein-1 (VAP1 inhibitor) resulted in improvement in UACR at week 12 in a phase 2 study[79].
- Gevokizumab and Canakinumab are IL-1-beta monoclonal antibodies. A study with gevokizumab was terminated; canakinumab showed no clinically meaningful improvement in either eGFR or UACR or renal adverse events[80].
- Emapticap pegol (CCL2-binding aptamer) showed no improvement in UACR[81].

Conclusion

There is increasing awareness of the importance of inflammation in the pathogenesis of DKD. Improved care of diabetic patients with respect to blood glucose and blood pressure control has improved CKD outcomes, but DKD remains the leading cause of ESRD worldwide. Further advances may require attention to other pathophysiologic mechanisms of DKD other than metabolic and hemodynamic alterations. Anti-inflammatory strategies may offer approaches of great interest in these patients.

References

1. Gheith O, Farouk N, Nampoory N, Halim MA, Al-Otaibi T. Diabetic kidney disease: worldwide difference of prevalence and risk factors. J Nephropharmacol. 2016; 5: 49-56.
2. Saran R, Robinson B, Abbott KC, Bragg-Gresham J, Chen X, Gipson D, Gu H, Hirth RA, Hutton D, Jin Y, et al. US Renal Data System 2019 Annual Data Report: Epidemiology of Kidney Disease in the United States. Am J Kidney Dis. 2020; 75: A6-7.
3. Gnudi L, Gentile G, Ruggenenti P. Oxford Textbook of Clinical Nephrology. 4 ed. Volume 2. Oxford University Press, Oxford, UK; 2016: 1199–1247.
4. Cravedi P, Remuzzi G. Pathophysiology of proteinuria and its value as an outcome measure in chronic kidney disease. Br J Clin Pharmacol. 2013; 76(4): 516–523.
5. Rossing K, Christensen PK, Hovind P, Tarnow L, Rossing P, Parving HH. Progression of nephropathy in type 2 diabetic patients. Kidney Int. 2004; 66(4): 1596–1605.
6. Kawabata N, Kawamura T, Utsunomiya K, Kusano E. High salt intake is associated with renal involvement in Japanese patients with type 2 diabetes mellitus. Intern Med. 2015; 54(3): 311–317.
7. Haffner S, Lehto S, Rönnemaa T, Pyörälä K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. N Engl J Med. 1998; 339(4): 229–234.
8. Afkarian M, Sachs M, Kestenbaum B, Hirsch I, Tuttle K, Himmelfarb J, de Boer IH. Kidney disease and increased mortality risk in type 2 diabetes. J Am Soc Nephrol. 2013; 24(2): 302–308.
9. Hasegawa G, Nakano K, Sawada M, Uno K, Shibayama Y, Ienaga K, Kondo M. Possible role of tumor necrosis factor and interleukin-1 in the development of diabetic nephropathy. Kidney Int. 1991; 40(6): 1007-1012.
10. Matoba K, Takeda Y, Nagai Y, Kawanami D, Utsunomiya K, Nishimura R. Unraveling the role of inflammation in the pathogenesis of diabetic kidney disease. Int J Mol Sci. 2019; 20(14). pii: E3393.
11. Nguyen D, Ping F, Mu W, Hill P, Atkins RC, Chadban SJ. Macrophage accumulation in human progressive diabetic nephropathy. Nephrology (Carlton) 2006; 11: 226–231.
12. Alexandraki K, Piperi C, Kalofoutis C, Singh J, Alaveras A, Kalofoutis A. Inflammatory process in type 2 diabetes: The role of cytokines. Ann N Y Acad Sci. 2006; 1084: 89-117.
13. Katsuki A, Sumida Y, Murashima S, Murata K, Takarada Y, Ito K, Fujii M, Tsuchihashi K, Goto H, Nakatani K, Yano Y. Serum levels of tumor necrosis factor-alpha are increased in obese patients with noninsulin-dependent diabetes mellitus. J Clin Endocrinol Metab. 1998; 83: 859–862.
14. Pickup JC, Chusney GD, Thomas SM, Burt D. Plasma interleukin-6, tumour necrosis factor alpha and blood cytokine production in type 2 diabetes. Life Sci. 2000; 67: 291–300.
15. Festa A, D'Agostino R, Howard G, Mykkänen L, Tracy RP, Haffner SM. Inflammation and microalbuminuria in nondiabetic and type 2 diabetic subjects: The Insulin Resistance Atherosclerosis Study. Kidney Int. 2000; 58: 1703–1710.
16. Bruno G, Merletti F, Biggeri A, Bargero G, Ferrero S, Pagano G, Cavallo Perin P; Casale Monferrato Study. Progression to overt nephropathy in type 2 diabetes: the Casale Monferrato Study. Diabetes Care 2003; 26: 2150–2155.
17. Elmarakby A, Sullivan J. Relationship between oxidative stress and inflammatory cytokines in diabetic nephropathy. Cardiovasc Ther. 2012; 30(1): 49–59.
18. Mora C, Navarro JF. Inflammation and diabetic nephropathy. Curr Diab Rep. 2006; 6: 463–468.
19. Leehey DJ. Targeting inflammation in diabetic kidney disease: Is there a role for pentoxifylline?
Kidney360. 2020; 1(4): 292-299.
20. Leehey DJ, Singh AK, Singh R. Angiotensin II and its receptors in diabetic nephropathy. In: Mogensen CE, Cortes P, eds. The Diabetic Kidney. Humana Press; 2006: 3-21.
21. Ziyadeh FN, Wolf G. Pathogenesis of the podocytopathy and proteinuria in diabetic glomerulopathy. Curr Diabetes Rev. 2008; 4(1): 39-45.
22. Pugliese G, Penno G, Natali A, Barutta F, Di Paolo S, Reboldi G, Gesualdo L, De Nicola L. Diabetic kidney disease: New clinical and therapeutic issues. Joint position statement of the Italian Diabetes Society and the Italian Society of Nephrology on "The natural history of diabetic kidney disease and treatment of hyperglycemia in patients with type 2 diabetes and impaired renal function". Nutr Metab Cardiovasc Dis. 2019; 29: 1127-1150.
23. Navarro J, Mora C. Role of inflammation in diabetic complications. Nephrol Dial Transplant. 2005; 20(12): 2601–2604.
24. Donate-Correa J, Tagua VG, Ferri C, Martín-Núñez E, Hernández-Carballo C, Ureña-Torres P, Ruiz-Ortega M, Ortiz A, Mora-Fernández C, Navarro-González JF. Pentoxifylline for renal

protection in diabetic kidney disease. A model of old drugs for new horizons. J Clin Med. 2019; 8(3). pii: E287.

25. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The Collaborative Study Group. N Engl J Med. 1993; 329: 1456-1462.

26. Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, Remuzzi G, Snapinn SM, Zhang Z, Shahinfar S. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med. 2001; 345: 861-869.

27. Sawaf H, Thomas G, Taliercio JJ, Nakhoul G, Vachharajani TJ, Mehdi A. Therapeutic advances in diabetic nephropathy. J Clin Med. 2022; 11: 378.

28. Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB, Ritz E, Atkins RC, Rohde R, Raz I. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med. 2001; 345: 851-860.

29. Cherney DZI, Perkins BA, Soleymanlou N, Har R, Fagan N, Johansen OE, Woerle H-J, von Eynatten M, Broedl UC. The effect of empagliflozin on arterial stiffness and heart rate variability in subjects with uncomplicated type 1 diabetes mellitus. Cardiovascular Diabetol. 2014; 13: 28.

30. Terami N, Ogawa D, Tachibana H, Hatanaka T, Wada J, Nakatsuka A, Eguchi J, Horiguchi CS, Nishii N, Yamada H, et al. Long-term treatment with the sodium glucose cotransporter 2 inhibitor, dapagliflozin, ameliorates glucose homeostasis and diabetic nephropathy in db/db mice. PLOS ONE. 2014; 9: e100777.

31. Kawanami D, Matoba K, Takeda Y, Nagai Y, Akamine T, Yokota T, Sango K, Utsunomiya K. SGLT2 inhibitors as a therapeutic option for diabetic nephropathy. Int J Mol Sci. 2017; 18: 1083.

32. Wanner C, Inzucchi SE, Lachin JM, Fitchett D, von Eynatten M, Mattheus M, Johansen OE, Woerle HJ, Broedl UC, Zinman B. Empagliflozin and progression of kidney disease in type 2 diabetes. N Engl J Med. 2016; 375: 323-334.

33. Nagata T, Fukuzawa T, Takeda M, Fukazawa M, Mori T, Nihei T, Honda K, Suzuki Y, Kawabe Y. Tofogliflozin, a novel sodium–glucose co-transporter 2 inhibitor, improves renal and pancreatic function in db/db mice. Br J Pharmacol. 2013; 170: 519-531.

34. Gembardt F, Bartaun C, Jarzebska N, Mayoux E, Todorov VT, Hohenstein B, Hugo C. The SGLT2 inhibitor empagliflozin ameliorates early features of diabetic nephropathy in BTBR ob/ob type 2 diabetic mice with and without hypertension. Am J Physiol Renal Physiol. 2014; 307: F317-F325.

35. Wang XX, Levi J, Luo Y, Myakala K, Herman-Edelstein M, Qiu L, Wang D, Peng Y, Grenz A, Lucia S, et al. SGLT2 protein expression is increased in human diabetic nephropathy: SGLT2 protein inhibition decreases renal lipid accumulation, inflammation, and the development of nephropathy in diabetic mice. J Biol Chem. 2017; 292: 5335-5348.

36. Ala M. SGLT2 inhibition for cardiovascular diseases, chronic kidney disease, and NAFLD. Endocrinol. 2021; 162(12): bqab157.

37. Cherney D, Lund SS, Perkins BA, Groop PH, Cooper ME, Kaspers S, Pfarr E, Woerle HJ, von Eynatten M. The effect of sodium glucose cotransporter 2 inhibition with empagliflozin on microalbuminuria and macroalbuminuria in patients with type 2 diabetes. Diabetologia. 2016; 59: 1860-1870.

38. Cherney DZI, Zinman B, Inzucchi SE, Koitka-Weber A, Mattheus M, von Eynatten M, Wanner C. Effects of empagliflozin on the urinary albumin-to-creatinine ratio in patients with type 2 diabetes and established cardiovascular disease: an exploratory analysis from the EMPA-REG OUTCOME randomised, placebo-controlled trial. Lancet Diabetes Endocrinol. 2017; 5: 610-621.

39. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, Shaw W, Law G, Desai M, Matthews DR. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med. 2017; 377: 644-657.

40. Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, Charytan DM, Edwards R, Agarwal R, Bakris G, Bull S, Cannon CP, Capuano G, Chu PL, de Zeeuw D, Greene T, Levin A, Pollock C, Wheeler DC, Yavin Y, Zhang H, Zinman B, Meininger G, Brenner BM, Mahaffey KW; CREDENCE Trial Investigators. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med. 2019; 380(24): 2295-2306.

41. Heerspink HJL, Stefánsson BV, Correa-Rotter R, Chertow GM, Greene T, Hou FF, Mann JFE, McMurray JJV, Lindberg M, Rossing P, Sjöström CD, Toto RD, Langkilde AM, Wheeler DC; DAPA-CKD Trial Committees and Investigators. Dapagliflozin in Patients with chronic kidney disease. N Engl J Med. 2020; 383(15): 1436-1446.

42. EMPA-KIDNEY Collaborative Group; Herrington WG, Staplin N, Wanner C, Green JB, Hauske SJ, Emberson JR, Preiss D, Judge P, Mayne KJ, Ng SYA, Sammons E, Zhu D, Hill M, Stevens W, Wallendszus K, Brenner S, Cheung AK, Liu ZH, Li J, Hooi LS, Liu W, Kadowaki T, Nangaku M, Levin A, Cherney D, Maggioni AP, Pontremoli R, Deo R, Goto

S, Rossello X, Tuttle KR, Steubl D, Petrini M, Massey D, Eilbracht J, Brueckmann M, Landray MJ, Baigent C, Haynes R; The EMPA-KIDNEY Collaborative Group. Empagliflozin in patients with chronic kidney disease. N Engl J Med. 2023; 388(2): 117-127.

43. Miller JA. Impact of hyperglycemia on the renin angiotensin system in early human type 1 diabetes mellitus. J Am Soc Nephrol. 1999; 10: 1778-1785.

44. Durvasula RV, Shankland SJ. Activation of a local renin angiotensin system in podocytes by glucose. Am J Physiol Renal Physiol. 2008; 294: F830-839.

45. Leehey DJ, Singh AK, Alavi N, Singh R. Role of angiotensin II in diabetic nephropathy. Kidney Int Suppl. 2000; 77: S93-S98.

46. Feng Q, Liu D, Lu Y, Liu Z. The interplay of renin-angiotensin system and toll-like receptor 4 in the inflammation of diabetic nephropathy. J Immunol Res. 2020; 2020: 6193407.

47. Schork A, Saynisch J, Vosseler A, Jaghutriz BA, Heyne N, Peter A, Häring HU, Stefan N, Fritsche A, Artunc F. Effect of SGLT2 inhibitors on body composition, fluid status and renin-angiotensin-aldosterone system in type 2 diabetes: a prospective study using bioimpedance spectroscopy. Cardiovasc Diabetol. 2019; 18: 46.

48. Fan YY, Kobori H, Nakano D, Hitomi H, Mori H, Masaki T, Sun YX, Zhi N, Zhang L, Huang W, et al. Aberrant activation of the intrarenal renin-angiotensin system in the developing kidneys of type 2 diabetic rats. Horm Metab Res. 2013; 45: 338-343.

49. Yoshimoto T, Furuki T, Kobori H, Miyakawa M, Imachi H, Murao K, Nishiyama A. Effects of sodium-glucose cotransporter 2 inhibitors on urinary excretion of intact and total angiotensinogen in patients with type 2 diabetes. J Investig Med. 2017; 65: 1057-1061.

50. Ansary TM, Nakano D, Nishiyama A. Diuretic effects of sodium glucose cotransporter 2 inhibitors and their influence on the renin-angiotensin system. Int J Mol Sci. 2019; 20(3): 629.

51. Nehme A, Zouein FA, Zayeri ZD, Zibara K. An update on the tissue renin angiotensin system and its role in physiology and pathology. J Cardiovasc Dev Dis. 2019; 6(2): 14.

52. Chen CM, Juan SH, Chou HC. Hyperglycemia activates the renin-angiotensin system and induces epithelial-mesenchymal transition in streptozotocin-induced diabetic kidneys. J Renin Angiotensin Aldosterone Syst. 2018; 19: 1470320318803009.

53. Leehey DJ, Carlson K, Reda DJ, Craig I, Clise C, Conner TA, Agarwal R, Kaufman JS, Anderson RJ, Lammie D, et al. Pentoxifylline in diabetic kidney disease (VA PTXRx): protocol for a pragmatic randomised controlled trial. BMJ Open. 2021; 11: e053019.

54. Navarro-González JF, Mora-Fernández C, Muros de Fuentes M, Chahin J, Méndez ML, Gallego E, Macía M, del Castillo N, Rivero A, Getino MA, et al. Effect of pentoxifylline on renal function and urinary albumin excretion in patients with diabetic kidney disease: the PREDIAN trial. J Am Soc Nephrol. 2015; 26: 220-229.

55. Shan D, Wu HM, Yuan QY, Li J, Zhou RL, Liu GJ. Pentoxifylline for diabetic kidney disease. Cochrane Database Syst Rev. 2012: Cd006800.

56. Leporini C, Pisano A, Russo E, G DA, de Sarro G, Coppolino G, Bolignano D. Effect of pentoxifylline on renal outcomes in chronic kidney disease patients: A systematic review and meta-analysis. Pharmacol Res. 2016; 107: 315-332.

57. Liu D, Wang LN, Li HX, Huang P, Qu LB, Chen FY. Pentoxifylline plus ACEIs/ARBs for proteinuria and kidney function in chronic kidney disease: a meta-analysis. J Int Med Res. 2017; 45: 383-398.

58. Agarwal R, Anker SD, Bakris G, Filippatos G, Pitt B, Rossing P, Ruilope L, Gebel M, Kolkhof P, Nowack C, et al. Investigating new treatment opportunities for patients with chronic kidney disease in type 2 diabetes: the role of finerenone. Nephrol Dial Transplant. 2022; 37: 1014-1023.

59. Farquharson CA, Struthers AD. Spironolactone increases nitric oxide bioactivity, improves endothelial vasodilator dysfunction, and suppresses vascular angiotensin I/angiotensin II conversion in patients with chronic heart failure. Circulation. 2000; 101: 594-597.

60. Kolkhof P, Jaisser F, Kim SY, Filippatos G, Nowack C, Pitt B. Steroidal and novel non-steroidal mineralocorticoid receptor antagonists in heart failure and cardiorenal diseases: comparison at bench and bedside. Handb Exp Pharmacol. 2017; 243: 271-305.

61. Davies JI, Band M, Morris A, Struthers AD. Spironolactone impairs endothelial function and heart rate variability in patients with type 2 diabetes. Diabetologia. 2004; 47: 1687-1694.

62. Pham JT, Schmitt BP, Leehey DJ. Effects of dual blockade of the renin angiotensin system in diabetic kidney disease: a systematic review and meta-analysis. J Nephrol Therapeutic 2012; S2. doi:10.4172/2161-0959.S2-003.

63. Amazit L, Le Billan F, Kolkhof P, Lamribet K, Viengchareun S, Fay MR, Khan JA, Hillisch A, Lombès M, Rafestin-Oblin ME, et al. Finerenone impedes aldosterone-dependent nuclear import of the mineralocorticoid receptor and prevents genomic recruitment of steroid receptor

coactivator-1. J Biol Chem. 2015; 290: 21876-21889.
64. Grune J, Beyhoff N, Smeir E, Chudek R, Blumrich A, Ban Z, Brix S, Betz IR, Schupp M, Foryst-Ludwig A, et al. Selective mineralocorticoid receptor cofactor modulation as molecular basis for finerenone's antifibrotic activity. Hypertension. 2018; 71: 599-608.
65. Lattenist L, Lechner SM, Messaoudi S, Le Mercier A, El Moghrabi S, Prince S, Bobadilla NA, Kolkhof P, Jaisser F, Barrera-Chimal J. Nonsteroidal mineralocorticoid receptor antagonist finerenone protects against acute kidney injury-mediated chronic kidney disease: role of oxidative stress. Hypertension. 2017; 69: 870-878.
66. Barrera-Chimal J, Estrela GR, Lechner SM, Giraud S, El Moghrabi S, Kaaki S, Kolkhof P, Hauet T, Jaisser F. The myeloid mineralocorticoid receptor controls inflammatory and fibrotic responses after renal injury via macrophage interleukin-4 receptor signaling. Kidney Int. 2018; 93: 1344-1355.
67. Bakris GL, Agarwal R, Chan JC, Cooper ME, Gansevoort RT, Haller H, Remuzzi G, Rossing P, Schmieder RE, Nowack C, et al. Effect of finerenone on albuminuria in patients with diabetic nephropathy: a randomized clinical trial. JAMA. 2015; 314: 884-894.
68. Rossing P, Filippatos G, Agarwal R, Anker SD, Pitt B, Ruilope LM, Chan JCN, Kooy A, McCafferty K, Schernthaner G, et al. Finerenone in predominantly advanced CKD and type 2 diabetes with or without sodium-glucose cotransporter-2 inhibitor therapy. Kidney Int Rep. 2022; 7: 36-45.
69. Ruilope LM, Pitt B, Anker SD, Rossing P, Kovesdy CP, Pecoits-Filho R, Pergola P, Joseph A, Lage A, Mentenich N, Scheerer MF, Bakris GL. Kidney outcomes with finerenone: An analysis from the FIGARO-DKD study. Nephrol Dial Transplant. 2022; gfac157. doi: 10.1093/ndt/gfac157.
70. Agarwal R, Filippatos G, Pitt B, Anker SD, Rossing P, Joseph A, Kolkhof P, Nowack C, Gebel M, Ruilope LM, Bakris GL; FIDELIO-DKD and FIGARO-DKD investigators. Cardiovascular and kidney outcomes with finerenone in patients with type 2 diabetes and chronic kidney disease: the FIDELITY pooled analysis. Eur Heart J. 2022; 43(6): 474-484.
71. Pergola PE, Raskin P, Toto RD, et al. Bardoxolone methyl and kidney function in CKD with type 2 diabetes. N Engl J Med 2011; 365: 327-336.
72. de Zeeuw D, Akizawa T, Audhya P, Bakris GL, Chin M, Christ-Schmidt H, Goldsberry A, Houser M, Krauth M, Lambers Heerspink HJ, et al. Bardoxolone methyl in type 2 diabetes and stage 4 chronic kidney disease. N Engl J Med. 2013; 369: 2492-2503.
73. Chin MP, Reisman SA, Bakris GL, O'Grady M, Linde PG, McCullough PA, Packham D, Vaziri ND, Ward KW, Warnock DG, et al. Mechanisms contributing to adverse cardiovascular events in patients with type 2 diabetes mellitus and stage 4 chronic kidney disease treated with bardoxolone methyl. Am J Nephrol. 2014; 39: 499-508.
74. Nangaku M, Kanda H, Takama H, Ichikawa T, Hase H, Akizawa T. Randomized clinical trial on the effect of bardoxolone methyl on gfr in diabetic kidney disease patients (TSUBAKI Study). Kidney Int Rep. 2020; 5: 879-890.
75. Chertow GM, Pergola PE, Chen F, Kirby BJ, Sundy JS, Patel UD. Effects of selonsertib in patients with diabetic kidney disease. J Am Soc Nephrol. 2019; 30: 1980-1990.
76. Hara A, Shimizu M, Hamaguchi E, Kakuda H, Ikeda K, Okumura T, Kitagawa K, Koshino Y, Kobayashi M, Takasawa K, et al. Propagermanium administration for patients with type 2 diabetes and nephropathy: A randomized pilot trial. Endocrinol Diabetes Metab. 2020; 3: e00159.
77. de Zeeuw D, Bekker P, Henkel E, Hasslacher C, Gouni-Berthold I, Mehling H, Potarca A, Tesar V, Heerspink HJ, Schall TJ. The effect of CCR2 inhibitor CCX140-B on residual albuminuria in patients with type 2 diabetes and nephropathy: a randomised trial. Lancet Diabetes Endocrinol. 2015; 3: 687-696.
78. Tuttle KR, Brosius FC, 3rd, Adler SG, Kretzler M, Mehta RL, Tumlin JA, Tanaka Y, Haneda M, Liu J, Silk ME, et al. JAK1/JAK2 inhibition by baricitinib in diabetic kidney disease: results from a Phase 2 randomized controlled clinical trial. Nephrol Dial Transplant. 2018; 33: 1950-1959.
79. de Zeeuw D, Renfurm RW, Bakris G, Rossing P, Perkovic V, Hou FF, Nangaku M, Sharma K, Heerspink HJL, Garcia-Hernandez A, et al. Efficacy of a novel inhibitor of vascular adhesion protein-1 in reducing albuminuria in patients with diabetic kidney disease (ALBUM): a randomised, placebo-controlled, phase 2 trial. Lancet Diabetes Endocrinol. 2018; 6: 925-933.
80. Ridker PM, MacFadyen JG, Glynn RJ, Koenig W, Libby P, Everett BM, Lefkowitz M, Thuren T, Cornel JH. Inhibition of interleukin-1β by canakinumab and cardiovascular outcomes in patients with chronic kidney disease. J Am Coll Cardiol. 2018; 71: 2405-2414.
81. Menne J, Eulberg D, Beyer D, Baumann M, Saudek F, Valkusz Z, Więcek A, Haller H. C-C motif-ligand 2 inhibition with emapticap pegol (NOX-E36) in type 2 diabetic patients with albuminuria. Nephrol Dial Transplant. 2017; 32: 307-315.