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DIFFERENT METABOLIC PATHWAYS IN DIABETIC KIDNEY DISEASE AND RECENT ADVANCES IN SLOWING DISEASE PROGRESSION

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ABSTRACT

Globally, diabetic kidney disease (DKD) is the leading cause of end-stage renal disease. As the most common microvascular complication of diabetes, DKD is a thorny, clinical problem in terms of its diagnosis and management. Intensive glucose control in DKD could slow down but not significantly halt disease progression. Revisiting the tremendous advances that have occurred in the field would enhance recognition of DKD pathogenesis as well as improve our understanding of translational science in DKD in this new era. In this review, we summarize advances in the understanding the local microenvironmental changes in diabetic kidneys and discuss the involvement of genetic factors in the pathogenesis of DKD. The review also focuses on understanding how the hemodynamic, metabolic, inflammatory, and alternative pathways are all entangled in pathogenesis of DKD and discuss various conventional and novel therapeutic targets that may play role in slowing DKD.

KEYWORDS: Diabetic Kidney Disease, Novel therapies, Pathogenesis.

1. INTRODUCTION

Diabetes has long been a growing epidemic in India and around the world. In 2011, there were 20.8 million people aged 18 years and older who carried a diagnosis of diabetes in the US alone.[1] There are estimated 72.96 million cases of diabetes in adult population of India. The prevalence in urban areas ranges between 10.9% and 14.2% and prevalence in rural India was 3.0-7.8% among population aged 20 years and above with a much higher prevalence among individuals aged over 50 years (INDIAB Study).[2] The number of adults aged 18–79 in the US that were newly diagnosed with diabetes has more than tripled from 493,000 in 1980 to over 1.5 million in 2011.[3] The increased prevalence of diabetes has also led to an increase in the number of macro- and microvascular complications of diabetes such as coronary heart disease, stroke, visual impairment, diabetic kidney disease (DKD), and end stage renal disease (ESRD). Over the past few decades, the prevalence of T2DM has steadily increased worldwide. In 2017, the International Diabetes Federation (IDF) predicted that there were 451 million people with diabetes worldwide, and the number was expected to increase to 693 million by 2045.[3] Among these diagnosed cases of diabetes, about 90% of patients have T2DM, and nearly half of T2DM patients eventually progress to chronic kidney disease (CKD).[4] Impressively, it was estimated that, among people aged 20e79 years, 425 million had diabetes, 50% were undiagnosed, and approximately 4.0 million died, which accounted for 14.5% of global all-cause mortality among people in this age range.[4] Additionally, diabetes remains the most common reason for progressing to end stage renal disease in the US and in many parts of the world.[4-6] The kidney is a vulnerable organ as well as the most important target of microvascular damage in both type 1 (T1DM) and type 2 diabetes mellitus (T2DM).[7-9] The first description of the association between diabetes and kidney damage in humans was in 1552 BC.[10,11] As the disease spectrum has changed around the world, DKD has become the single most frequent cause of ESRD at daunting rates over the past 30 years, in both developed and developing countries.[12-18]

2. HISTOPATHOPHYSIOLOGY AND HEMODYNAMIC PATHWAYS OF DKD

The histopathologic changes of DKD have been well documented previously and will not be described in

detail here, Ultrastructurally, podocytes suffer hypertrophy and then foot process effacement which leads to functional changes such as increased albumin excretion.[19,20] It should be noted that, in patients with type 2 diabetes, GFR loss can occur independently of albuminuria[21,22] and it has been demonstrated that microalbuminuria is observed in only 45% of this population.[23] The histopathologic change of DKD has been attributed to diabetic macroangiopathy as opposed solely to microangiopathy and has also been attributed to aging, atherosclerosis, hypertension, and episodes of acute kidney injury.[24] Activation of the RAS leads to increased angiotensin II levels which subsequently cause efferent arteriolar vasoconstriction. Elevated levels of angiotensin II are associated with increased albuminuria and nephropathy in both humans and mice.[25,26] ACEIs and ARBs have a long track record in reducing the doubling rate of creatinine, albuminuria, and progression to nephropathy, ESRD, and death.[27] Another potent vasoconstrictor of the efferent arteriole is endothelin-1 (ET-1). ET-1 has various physiologic functions in the kidney that mimic RAS including mediating vasoconstriction and hence playing a role in hypertension, endothelial dysfunction, inflammation, and fibrosis.[28] Additionally, increased ET-1 expression activates a signaling cascade which leads to mesangial cell hypertrophy and proliferation as well as extracellular matrix (ECM) production. It is also thought to activate receptors that directly increase glomerular permeability, hence leading to worsening albuminuria and progression of DKD.[28]

3. METABOLIC PATHWAYS OF DKD

In T2DM, Beta cell failure, mitochondria dysfunction[29,30], abnormal endoplasmic reticulum stress[31,32], and declined autophagic activity have been implicated as potential causes of insulin resistance.[33] However, as the major microvascular complication of T2DM, the pathogenesis of DKD is complex and multifactorial. Traditionally, the initiation of DKD was thought to be induced mostly by hemodynamic changes and metabolic disorders. These alterations subsequently cause activation of the renin-angiotensin-aldosterone system (RAAS)[34-36], increased excretion of metabolic products, proinflammatory/profibrotic growth factors/chemo-cytokines, and dysregulation of a number of intracellular signalling cascades that are associated with oxidative stress[36-41], inflammation[42-44], and fibrosis[45-48], as well as the complement system.[49] In 2001 Brownlee explained about this pathway,[50] He helped to clarify that hyperglycemia leads to increased glycolysis which then upregulates four distinct entities: the polyol pathway, hexosamine pathway, production of advanced glycation end products (AGEs), and activation of protein kinase C (PKC). Glyceraldehyde-3-phosphate dehydrogenase (GADPH) converts glyceraldehyde3-phosphate to 1,3-diphosphoglycerate is inhibited by excess superoxide produced by the electron-transport chain which occurs in the setting of hyperglycemia.[51,52] Inhibition of GADPH prevents glycolysis from taking place and causes an upregulation of upstream components of glycolysis, specifically glucose, glucose-6-phosphate, and fructose-6-phosphate.

4. GENETIC RISK FACTORS

From a genetic standpoint, diabetes can be classified into two categories: monogenic, including neonatal diabetes mellitus and maturity onset diabetes of the young, and polygenic, including T1DM and T2DM. Until now, in the clinic, it was clear that T2DM-induced DKD does not develop in all T2DM patients, even those with poor long-term glycemic control and lifestyle intervention. It is noteworthy that diabetic patients who have a family history of hypertension or cardiovascular disease are more likely to develop DKD.[53-56] This fact supports the idea that genetic factors may play central roles in the predisposition of T2DM-DKD. In T2DM-DKD, genetic susceptibility is mainly evidenced by familial aggregation, and the prevalence of DKD varies among different racial and ethnic groups.[57] In the 1980s, a pioneering genetic study of DKD was reported in a small study of families having two or more siblings diagnosed with T1DM.[58]

5. DRUG TARGETS IN DKD

Currently, the available therapies for DKD include treatment of hypertension with RAS inhibition, glycemic control, and dietary interventions. Inhibition of the RAS has been the primary therapeutic intervention for DKD for two decades. Several clinical trials demonstrated that administration of single RAS inhibitors, angiotensin II receptor blockers (ARBs), or ACE inhibitors was modestly renal-protective in patients with DKD and "overt proteinuria/macroalbuminuria" (generally, urine proteinto-creatinine ratio >500 mg/g or albumin-to-creatinine ratio >300 mg/g)[59-61] Aldose reductase inhibitors prevent the conversion of glucose to sorbitol by inhibiting the enzyme aldose reductase. Epalrestat was shown to prevent mesangial expansion and improve urine albumin excretion in diabetic rats.[62]

6. RISK OF RAS DUAL THERAPY IN DKD – REASON FOR NOVAL THERAPIES

Combination therapy with two agents (e.g., ACE inhibitor, ARB, and/or a direct renin inhibitor) may be synergistic and result in greater renal protection.[63,64] These clinical trials were stopped early because of safety concerns and high rates of adverse events, particularly hyperkalemia and acute kidney injury with dual therapy.[65] There were no apparent benefits on outcomes from combination therapy. However, the trials were stopped prematurely, the efficacy results from these trials are inconclusive. Despite evidence that single RAS inhibition with either an ARB or an ACE inhibitor can reduce the risk of DKD progression, there is increased risk of adverse events with dual RAS blockade and no obvious additional benefit of this form of combination therapy in recent clinical trials. Development of RAS-independent therapies is an important direction for future work.[65,66]

7. THERAPEUTIC AGENTS TARGETING THE HEMODYNAMIC PATHWAY

In general, the natural history of DKD could be divided into five stages: the initial increased GFR due to hyperfiltration, the 'silent' phase, the 'incipient' phase, the 'overt' phase, and eventual development of ESRD.[67] However, it is clear that not all T2DM patients exactly follow this classic pattern of the development of kidney complications. Based on the United Kingdom Prospective Diabetes Study (UKPDS) report, after a median of 15 years of follow-up after T2DM diagnosis, 38% of enrolled patients developed albuminuria and 29% developed renal dysfunction.[68] Impressively, of those participants who developed kidney impairment, 61% did not have preceding albuminuria and 39% never developed albuminuria during the study. It should be noted that some DKD patients present with impaired GFR and no albuminuria because the timing of T2DM onset in these patients is often unknown and early onset of DKD may reflect a long silent period. The potential GFR decline with age and albuminuria could be masked due to treatments of hypertension. Currently, although the overall prevalence of diabetes-associated kidney diseases is increasing, it is in part attributable to the presence of nondiabetic kidney diseases (NDKD) such as various primary or secondary forms of glomerulonephritis, which may not be suspected on the basis of clinical signs or urine abnormalities.[69] Therefore, CKD in a T2DM patient may represent true DKD, NDKD, or mixed forms of DKD and NDKD. Of note, the prevalence of DKD and NDKD varies significantly among T2DM-DKD patients receiving renal biopsy from different institutions worldwide.[69] To some extent, these kinds of continuously evolving paradigms of development of kidney diseases in T2DM patients make it difficult for physicians to make a precise diagnosis of DKD. Renal biopsy remains the current most reliable. ET-1 antagonists first showed promise in diabetic rat models when they were compared to ACEI and had significantly decreased renal glomerular diameter and deposition of eosinophilic material within glomeruli.[70] In another experimental model, the ET-1 antagonist avosentan demonstrated attenuated mesangial and glomerular matrix protein accumulation as well as normalization in creatinine clearance; these findings were comparable or superior to mice that had been randomized to ACEI.[71] The ASCEND trial was a multinational, double-blind, placebo-controlled trial which randomized patients with type 2 diabetes with overt nephropathy to avosentan or placebo in addition to continued RAS-inhibition. Although the trial was stopped prematurely due to an excess of cardiovascular events in the intervention group, there was a dose-dependent reduction in albuminuria in the avosentan group[72] when compared to the placebo arm. A post hoc analysis of the ASCEND trial found that the increased events of congestive heart failure (CHF) were preceded by increases in body weight and that future trials with ET-1 receptor antagonists would benefit from close monitoring of body weight to sooner identify any potential CHF development.[73] In a more recent study, data from two-phase 2b, randomized, double-blind, placebo controlled trials in patients with type 2 diabetes with overt nephropathy were pooled to compare concomitant atrasentan and RAS-inhibitor use with a placebo group. Compared to placebo, the atrasentan/RAS inhibitor group had a dose dependent improvement in albuminuria. While there was also a significant increase in body weight, the rates of cardiovascular events did not differ between the groups.[74] The SONAR trial is currently undergoing large-scale recruitment and will evaluate the effect of concomitant administration of atrasentan and RAS inhibitor on firm clinical endpoints such as the first occurrence to a composite renal endpoint, doubling of serum creatinine, or the onset of ESRD.[75] Two newly emerged agents, sodium-glucose cotransporter 2 (SGLT-2) inhibitors and glucagon-like peptide 1 (GLP-1) receptor agonists, have been incorporated into clinical practice for their renoprotective capacity in reducing glycemia, blood pressure, body weight, albuminuria, and GFR decline in T2DM patients, especially in those patients in moderate to severe stages of DKD.[76] Mechanistically, SGLT2 is a low affinity, high capacity glucose transporter distributed in renal proximal tubules. It is responsible for 90% of glucose reabsorption.[77]

8. IMPORTANCE OF GLYCEMIC CONTROL

Glycemic control is essential to the optimal management of diabetes and prevention of complications, including DKD in both type 1 and type 2 diabetes A strong positive association between A1C concentration and incident DKD was found after 11 years of follow-up in type 2 diabetes in the Atherosclerosis Risk in Communities study.[78] The association was present in the absence of albuminuria and retinopathy at baseline. Similar to the DCCT/EDIC in type 1 diabetes, several studies in relatively early-onset type 2 diabetes found that controlling hyperglycemia (to an A1C of ~7% vs. an A1C of ~9%) prevented new-onset and progressive albuminuria.[79]

9. DRUG TARGETS THAT INHIBITS AGEs

Primary among the aberrant metabolic products that drive the DKD processare advanced glycation end products (AGEs) and reactive oxygen species (ROS). These products are key activators for upregulation of proinflammatory and pro-fibrotic mediator production. Multiple cell types produce these mediators, ultimately resulting in the pathogenesis of DKD, AGEs are modified proteins, peptides, and amino acids that are nonenzymatically glycated and oxidized after interaction of amino groups with aldose sugars. AGEs increase in hyperglycemic conditions and after consumption of foods high in protein, especially animal meats cooked at high temperatures. AGEs are increased in the kidneys of patients with DKD, and serum levels of AGEs correlate with DKD severity.[80] Pyridoxamine (PDX), a derivative of vitamin B6, inhibits the formation of AGEs. In two different rodent models of DKD, administration of PDX

improved albuminuria and attenuated increases in serum creatinine.[81] In an analysis of pooled data from two phase II clinical trials of PDX for 24 weeks' duration in people with DKD and overt proteinuria, increases in serum creatinine levels were attenuated.

10. SODIUM-GLUCOSE COTRANSPORTER 2 IN DKD

sodium-glucose cotransporter 2 (SGLT2) inhibitors are of potential therapeutic benefit in DKD. They inhibit the reabsorption of glucose in the proximal tubule, reduce HbA1c levels by 0.5–1%[82], and contribute to weight loss as a result of glucosuria andimprove systolic anddiastolic blood pressures as a result of osmotic diuresis.[83,84] In diabetic mouse models, dapagliflozin, a SGLT2 inhibitor, reduced hyperglycemia, albuminuria, the expression of inflammatory cytokines and oxidative stress, glomerular mesangial expansion, and interstitial fibrosis when compared to controls. Currently, two gliflozins, canagliflozin and dapagliflozin, have been approved by the FDA for use in the treatment of type 2 diabetes.

11. DRUGS THAT TARGET ON INFLAMMATORY PATHWAYS

As we know, NF-κB expression in the kidney is associated with inflammation and cell death and leads to interstitial cell infiltration and proteinuria. In diabetic rat models, the thiazolidinedione, pioglitazone, was shown to decrease expression of TGF-β, type IV collagen, and ICAM-1,[85] 1,25-Dihydroxyvitamin D3 has been shown to block hyperglycemia-induced renal injury by inhibiting NF-κB activation in vitro.[86] In humans, there have also been various small studies showing that vitaminD3 has anantiproteinuric effect in patients with diabetes.[87-89] It remains to be seen whether the antiproteinuric effect is due primarily to NF-κB inhibition or a combination of effects from vitamin D. The Janus kinase/signal transducers and activators of transcription (JAK/STAT) signaling pathway is a way for chemical signals outside of a cell to be relayed to gene promoters at the DNA level. JAK2 is present in renal and vascular tissue.[90] It is activated by ROS caused by hyperglycemic states and is associated with hypertrophy of mesangial cells.[91] The JAK/STAT pathway was shown to be inhibited by suppressors of cytokine signaling (SOCS) proteins. Increased expression of SOCS1 and SOCS3 was seen in biopsies of patients with DKD when compared to those with minimal change disease.[92] When SOCS1 and SOC3 adenovirus were delivered into the kidneys of diabetic rats, their renal function significantly improved; they had decreased mesangial expansion, fibrosis, and influx of macrophages, as well as decreased expression of inflammatory and profibrotic proteins.[92] It is unclear if the JAK/STAT pathway will ever be a reasonable target for therapeutics in DKD given its ubiquitous presence in the body and the potential for adverse effects.[61] However, JAK/STAT pathway inhibitors have a long history of safety and efficacy in autoimmune diseases such as rheumatoid arthritis. Baricitinib (LY3009104) is a JAK1/JAK2 inhibitor that initially developed to treat rheumatoid arthritis and is now also being evaluated in a phase 2 study for patients with DKD.[93]

12. NON PHARMACOLOGICAL APPROACHES ON INFLAMMATORY PATHWAYS

Interestingly, various complementary therapeutics have been pursued in the quest for improving DKD, including milk thistle, turmeric, and green tea. Silymarin is the main active component found in seeds of milk thistle and has been used since ancient times for a variety of ailments; it is thought to have powerful anti-inflammatory, antioxidant, and antifibrotic properties.[94] In a randomized, doubleblind, placebo-controlled trial of 60 patients with type 2 diabetes with macroalbuminuria, silymarin was found to significantly reduce albuminuria and urinary and serum levels of TNF-α and malondialdehyde, the latter being a marker of oxidative stress, when compared to controls.[94] Turmeric is a popular South Asian spice of the ginger family and has been shown in experimental models to reduce expression of both TGF-β and IL-8.[95,96] In a randomized, double-blind, placebo-controlled trial of 40 patients with type 2 diabetes with overt nephropathy, those randomized to curcumin, the active ingredient in turmeric, were noted to have significantly decreased proteinuria, serum levels of TGF-β, and serum and urinary levels of IL-8 when compared to controls.[97]

CONCLUSION

DKD is a multifactorial diabetic complication with numerous mechanistic pathways contributing to disease pathogenesis. Despite the tremendous advancement in delineating these pathways that contribute to DKD, clinicians are still a long way away from having a new drug in their prescribing guidelines. Many of the above therapeutics have been successful in experimental models, yet few have proven sufficiently efficacious to be brought into the mainstream management of DKD, more attention is now paid to genetic risk factors and epigenetic modification in DKD development. Emerging valuable tools are ready for constructing multiple bridges among translational, precision, and personalize medicine of DKD in the clinic. Ultimately, the treatment of DKD will likely require a multifaceted approach given the numerous pathways involved in the diabetic kidney.

REFERENCES

1. Number (in Millions) of Civilian, Non institutionalized Adults with Diagnosed Diabetes, United States, 1980–2011, http://www .cdc.gov/diabetes/statistics/prev/national/figadults.htm
2. Ranjit Mohan Anjana, Mohan Deepa et al Prevalence of diabetes and prediabetes in 15 states of India: results from the ICMR–INDIAB population-based cross-sectional study, The Lancet Diabetes & Endocrinology, 2017; 5(8): 585-596.

3. Centers for Disease Control and Prevention,Annual Number (in Thousands) of New Cases of Diagnosed Diabetes Among Adults Aged 18–79 Years, United States, 1980–2011, Centers for Disease Control and Prevention, 2012, http://www.cdc.gov/diabetes/statistics/incidence/fig1.htm.
4. Haiyan Fu, Silvia Liu, Sheldon I. Bastacky, Xiaojie Wang, Xiao-Jun Tian, Dong Zhou, Diabetic kidney diseases revisited: A new perspective for a new era, MOLECULAR METABOLISM, 2019; 30: 250-263.
5. E. Ritz, I. Rychlik, F. Locatelli, and S. Halimi, "End-stage renal failure in type 2 diabetes: a medical catastrophe of worldwide dimensions," American Journal of Kidney Diseases, 1999; 34(5): 795–808.
6. A. T. Reutens, "Epidemiology of Diabetic Kidney Disease," Medical Clinics of North America, 2013; 97(1): 1–18.
7. Thomas, M.C., Brownlee, M., Susztak, K., Sharma, K., Jandeleit-Dahm, K.A., Zoungas, S., et al., 2015. Diabetic kidney disease. Nature Reviews Disease Primers, 1: 15018.
8. Bjerg, L., Hulman, A., Carstensen, B., Charles, M., Jorgensen, M.E., Witte, D.R., 2018. Development of microvascular complications and effect of concurrent risk factors in type 1 diabetes: a multistate model from an observational clinical cohort study. Diabetes Care, 41: 2297e2305.
9. Valencia, W.M., Florez, H., 2017. How to prevent the microvascular complications of type 2 diabetes beyond glucose control. BMJ British Medical Journal, 356.
10. Cameron, J.S., 2006. The discovery of diabetic nephropathy: from small print to centre stage. Journal of Nephrology, 19(Suppl 10): S75eS87.
11. Alicic, R.Z., Rooney, M.T., Tuttle, K.R., 2017. Diabetic kidney disease: challenges, progress, and possibilities. Clinical Journal of the American Society of Nephrology, 12: 2032e2045.
12. Afkarian, M., Zelnick, L.R., Hall, Y.N., Heagerty, P.J., Tuttle, K., Weiss, N.S., et al., 2016. Clinical manifestations of kidney disease among US adults with diabetes, 1988-2014. JAMA 316: 602e610.
13. Low, S.K.M., Sum, C.F., Yeoh, L.Y., Tavintharan, S., Ng, X.W., Lee, S.B.M., et al., 2015. Prevalence of chronic kidney disease in adults with type 2 diabetes mellitus. Annals Academy of Medicine Singapore, 44: 164e171.
14. Thomas, B., van Pelt, M., Mehrotra, R., Robinson-Cohen, C., LoGerfo, J., 2014. An estimation of the prevalence and progression of chronic kidney disease in a rural diabetic cambodian population. PLoS One, 9: e86123.
15. Thomas, M.C., Weekes, A.J., Broadley, O.J., Cooper, M.E., Mathew, T.H., 2006. The burden of chronic kidney disease in Australian patients with type 2 diabetes (the NEFRON study). Medical Journal of Australia, 185: 140e144.
16. Prasannakumar, M., Rajput, R., Seshadri, K., Talwalkar, P., Agarwal, P., Gokulnath, G., et al., 2015. An observational, cross-sectional study to assess the prevalence of chronic kidney disease in type 2 diabetes patients in India (START -India). Indian J Endocrinol Metab, 19: 520e523.
17. Zhang, L., Wang, F., Wang, L., Wang, W., Liu, B., Liu, J., et al., 2012. Prevalence of chronic kidney disease in China: a cross-sectional survey. Lancet, 379: 815e822.
18. Cho, N.H., Shaw, J.E., Karuranga, S., Huang, Y., da Rocha Fernandes, J.D., Ohlrogge, A.W., et al., 2018. IDF Diabetes Atlas: global estimates of diabetes prevalence for 2017 and projections for 2045. Diabetes Research and Clinical Practice, 138: 271e281.
19. K. Reidy, H. M. Kang, T. Hostetter, and K. Susztak, "Molecular mechanisms of diabetic kidney disease," Journal of Clinical Investigation, 2014; 124(6): 2333–2340.
20. A. K. H. Lim, "Diabetic nephropathy—complications and treatment," International Journal of Nephrology and Renovascular Disease, 2014; 7: 361–381.
21. R. Z. Alicic and K. R. Tuttle, "Novel therapies for diabetic kidney disease," Advances in Chronic Kidney Disease, 2014; 21(2): 121–133.
22. G. Pugliese, "Updating the natural history of diabetic nephropathy," Acta Diabetologica, 2014; 51(6): 905–915.
23. H. J. Kramer, Q. D. Nguyen, G. Curhan, and C.-Y. Hsu, "Renal insufficiency in the absence of albuminuria and retinopathy among adults with type 2 diabetes mellitus," The Journal of the American Medical Association, 2003; 289(24): 3273–3277.
24. P. Fioretto, M. L. Caramori, and M. Mauer, "The kidney in diabetes: dynamic pathways of injury and repair. The Camillo Golgi Lecture 2007," Diabetologia, 2008; 51(8): 1347–1355.
25. W. Huang, Y. Gallois, N. Bouby et al., "Genetically increased angiotensin I-converting enzyme level and renal complications in the diabetic mouse," Proceedings of the National Academy of Sciences of the United States of America, 2001; 98(23): 13330–13334.
26. S. Rudberg, L. M. Rasmussen, H.-J. Bangstad, and R. Osterby, "Influence of insertion/deletion polymorphism in the ACE-I gene on the progression of diabetic glomerulopathy in type 1 diabetic patients with microalbuminuria," Diabetes Care, 2000; 234: 544–548.
27. W. A. Wilmer, L. A. Hebert, E. J. Lewis et al., "Remission of nephrotic syndrome in type 1 diabetes: long-term follow-up of patients in the captopril study," American Journal of Kidney Diseases, 1999; 34(2): 308–314.
28. K. Benz and K. Amann, "Endothelin in diabetic renal disease," Contributions to Nephrology, 2011; 172: 139–148.
29. Sharma, K., Karl, B., Mathew, A.V., Gangoiti, J.A., Wassel, C.L., Saito, R., et al., 2013. Metabolomics reveals signature of mitochondrial dysfunction in

diabetic kidney disease. Journal of the American Society of Nephrology, 24: 1901e1912.
30. Czajka, A., Ajaz, S., Gnudi, L., Parsade, C.K., Jones, P., Reid, F., et al., 2015. Altered mitochondrial function, mitochondrial DNA and reduced metabolic flexibility in patients with diabetic nephropathy. EBio Medicine, 2: 499e512.
31. Lindenmeyer, M.T., Rastaldi, M.P., Ikehata, M., Neusser, M.A., Kretzler, M., Cohen, C.D., et al., 2008. Proteinuria and hyperglycemia induce endoplasmic reticulum stress. Journal of the American Society of Nephrology, 19: 2225e 2236.
32. Brosius, F.C., Kaufman, R.J., 2008. Is the ER stressed out in diabetic kidney disease? Journal of the American Society of Nephrology, 19: 2040e2042.
33. Barlow, A.D., Thomas, D.C., 2015. Autophagy in diabetes: beta-cell dysfunction, insulin resistance, and complications. DNA and Cell Biology, 34: 252e260.
34. Gurley, S.B., Coffman, T.M., 2007. The renin-angiotensin system and diabetic nephropathy. Seminars in Nephrology, 27: 144e152.
35. Molnar, A., Koszegi, S., Lenart, L., Hodrea, J., Balogh, D., Szkibinszkij, E., et al., 2018. The renin-angiotensin-aldosterone system inhibitors ameliorate hyperglycaemia induced tubulointersitial fibrosis in diabetic nephropathy. Nephrology Dialysis Transplantation, 33: 179.
36. Rahimi, Z., 2016. The role of renin angiotensin aldosterone system genes in diabetic nephropathy. Canadian Journal of Diabetes, 40: 178e183.
37. Sharavana, G., Joseph, G.S., Baskaran, V., 2017. Lutein attenuates oxidative stress markers and ameliorates glucose homeostasis through polyol pathway in heart and kidney of STZ-induced hyperglycemic rat model. European Journal of Nutrition, 56: 2475e2485.
38. Kumar Pasupulati, A., Chitra, P.S., Reddy, G.B., 2016. Advanced glycation end products mediated cellular and molecular events in the pathology of diabetic nephropathy. Biomolecular Concepts, 7: 293e309.
39. Buse, M.G., 2006. Hexosamines, insulin resistance, and the complications of diabetes: current status. American Journal of Physiology, Endocrinology and Metabolism, 290: E1eE8.
40. Geraldes, P., King, G.L., 2010. Activation of protein kinase C isoforms and its impact on diabetic complications. Circulation Research, 106: 1319e1331.
41. Idris-Khodja, N., Ouerd, S., Mian, M.O.R., Gornitsky, J., Barhoumi, T., Paradis, P., et al., 2016. Endothelin-1 overexpression exaggerates diabetesinduced endothelial dysfunction by altering oxidative stress. American Journal of Hypertension, 29: 1245e1251.
42. Liu, Y.N., Zhou, J.W., Li, T.T., Wu, J., Xie, S.H., Liu, H.F., et al., 2017. Sulodexide protects renal tubular epithelial cells from oxidative stressinduced injury via upregulating klotho expression at an early stage of diabetic kidney disease. Journal of Diabetes Research, 2017: 4989847.
43. Marrero, M.B., Banes-Berceli, A.K., Stern, D.M., Eaton, D.C., 2006. Role of the JAK/STAT signaling pathway in diabetic nephropathy. American Journal of Physiology e Renal Physiology, 290: F762eF768.
44. Anderberg, R.J., Meek, R.L., Hudkins, K.L., Cooney, S.K., Alpers, C.E., Leboeuf, R.C., et al., 2015. Serum amyloid A and inflammation in diabetic kidney disease and podocytes. Laboratory Investigation, 95: 250e262.
45. Suryavanshi, S.V., Kulkarni, Y.A., 2017. NF-kappabeta: a potential target in the management of vascular complications of diabetes. Frontiers in Pharmacology, 8: 798.
46. Deshpande, S.D., Putta, S., Wang, M., Lai, J.Y., Bitzer, M., Nelson, R.G., et al., 2013. Transforming growth factor-beta-induced cross talk between p53 and a MicroRNA in the pathogenesis of diabetic nephropathy. Diabetes, 62: 3151e3162.
47. Li, L., Chen, L., Zang, J., Tang, X., Liu, Y., Zhang, J., et al., 2015. C3a and C5a receptor antagonists ameliorate endothelial-myofibroblast transition via the Wnt/beta-catenin signaling pathway in diabetic kidney disease. Metabolism, 64: 597e610.
48. Li, S.Y., Huang, P.H., Tarng, D.C., Lin, T.P., Yang, W.C., Chang, Y.H., et al., 2015. Four-and-a-Half LIM domains protein 2 is a coactivator of Wnt signaling in diabetic kidney disease. Journal of the American Society of Nephrology, 26: 3072e3084.
49. Ahn, S.H., Susztak, K., 2010. Getting a notch closer to understanding diabetic kidney disease. Diabetes, 59: 1865e1867.
50. Flyvbjerg, A., 2017. The role of the complement system in diabetic nephropathy. Nature Reviews Nephrology, 13: 311e318.
51. M. Brownlee, "Biochemistry and molecular cell biology of diabetic complications," Nature, 2001; 414(6865): 813–820.
52. X.-L. Du, D. Edelstein, L. Rossetti et al., "Hyperglycemiainduced mitochondrial superoxide overproduction activates the hexosamine pathway and induces plasminogen activator inhibitor-1 expression by increasing Sp1 glycosylation," Proceedings of the National Academy of Sciences of the United States of America, 2000; 97(22): 12222–12226.
53. T. Nishikawa, D. Edelstein, X. L. Du et al., "Normalizing mitochondrial superoxide production blocks three pathways of hyperglycaemic damage," Nature, 2000; 404(6779): 787–790.
54. Yeung, E.H., Pankow, J.S., Astor, B.C., Powe, N.R., Saudek, C.D., Kao, W.H., 2007. Increased risk of type 2 diabetes from a family history of coronary heart disease and type 2 diabetes. Diabetes Care, 30: 154e156.
55. Fava, S., Hattersley, A.T., 2002. The role of genetic susceptibility in diabetic nephropathy: evidence

from family studies. Nephrology Dialysis Transplantation, 17: 1543e1546.
56. Tedla, F.M., Brar, A., Browne, R., Brown, C., 2011. Hypertension in chronic kidney disease: navigating the evidence. International Journal of Hypertension, 2011: 132405.
57. Canani, L.H., Gerchman, F., Gross, J.L., 1998. Increased familial history of arterial hypertension, coronary heart disease, and renal disease in Brazilian type 2 diabetic patients with diabetic nephropathy. Diabetes Care, 21: 1545e1550.
58. Davis, T.M.E., Coleman, R.L., Holman, R.R., Grp, U., 2014. Ethnicity and longterm vascular outcomes in Type 2 diabetes: a prospective observational study (UKPDS 83). Diabetic Medicine, 31: 200e207.
59. Seaquist, E.R., Goetz, F.C., Rich, S., Barbosa, J., 1989. Familial clustering of diabetic kidney disease. Evidence for genetic susceptibility to diabetic nephropathy. New England Journal of Medicine, 320: 1161e1165.
60. Brenner BM, Cooper ME, de Zeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med, 2001; 345: 861–869.
61. Amann B, Tinzmann R, Angelkort B. ACE inhibitors improve diabetic nephropathy through suppression of renal MCP-1. Diabetes Care, 2003; 26: 2421–2425.
62. Sjolie AK, Chaturvedi N, Fuller J. [Effect of lisinopril on progression of retinopathy and microalbuminuria in normotensive subjects with insulin-dependent diabetes mellitus]. Ugeskrift for laeger, 1999; 161: 949–952.
63. Itagaki, K. Shimizu, Y. Kamanaka et al., "The effect of an aldose reductase inhibitor (Epalrestat) on diabetic nephropathy in rats," Diabetes Research and Clinical Practice, 1994; 25(3): 147–154.
64. Fried LF, Emanuele N, Zhang JH, et al. Combined angiotensin inhibition for the treatment of diabetic nephropathy. N Engl J Med, 2013; 369: 1892–1903.
65. Mann JF, Schmieder RE, McQueen M, et al. Renal outcomes with telmisartan, ramipril, or both, in people at high vascular risk (the ONTARGET study): a multicentre, randomised, double-blind, controlled trial. Lancet, 2008; 372: 547–553.
66. Parving HH, Brenner BM, McMurray JJ, et al. Cardiorenal end points in a trial of aliskiren for type 2 diabetes. N Engl J Med, 2012; 367: 2204–2213.
67. Brad P. Dieter, Radica Z. Alicic, Rick L. Meek, Robert J. Anderberg, Sheryl K. Cooney and Katherine R. Tuttle, Novel Therapies for Diabetic Kidney Disease: Storied Past and Forward Paths, Summer 2015; 28(3): 167-174.
68. Zagkotsis, G., Markou, M., Paschou, E., Papanikolaou, P., Sabanis, N., 2018. Preventing the development and progression of diabetic kidney disease: where do we stand? Diabetes Metab Syndr, 12: 585e590.
69. Retnakaran, R., Cull, C.A., Thorne, K.I., Adler, A.I., Holman, R.R., Group, U.S., 2006. Risk factors for renal dysfunction in type 2 diabetes: U.K. Prospective Diabetes Study 74. Diabetes, 55: 1832e1839
70. Anders, H.J., Huber, T.B., Isermann, B., Schiffer, M., 2018. CKD in diabetes: diabetic kidney disease versus nondiabetic kidney disease. Nature Reviews Nephrology, 14: 361e377.
71. S. Dhein, S. Hochreuther, C. A. D. Spring, K. Bollig, C. Hufnagel, and M. Raschack, "Long-term effects of the endothelin(A) receptor antagonist LU 135252 and the angiotensinconverting enzyme inhibitor trandolapril on diabetic angiopathy and nephropathy in a chronic type I diabetes mellitus rat model," Journal of Pharmacology and Experimental Therapeutics, 2000; 293(2): 351–359.
72. A. M. D. Watson, J. Li, C. Schumacher et al., "The endothelin receptor antagonist avosentan ameliorates nephropathy and atherosclerosis in diabetic apolipoprotein e knockout mice," Diabetologia, 2010; 53(1): 192–203.
73. F. E. Mann, D. Green, K. Jamerson et al., "Avosentan for overt diabetic nephropathy," Journal of the American Society of Nephrology, 2010; 21(3): 527–535.
74. Hoekman, H. J. Lambers Heerspink, G. Viberti, D. Green, J. F. E. Mann, and D. De Zeeuw, "Predictors of congestive heartfailure after treatment with an endothelin receptor antagonist," Clinical Journal of the American Society of Nephrology, 2014; 9(3): 490–498.
75. D. de Zeeuw, B. Coll, D. Andress et al., "The endothelin antagonist atrasentan lowers residual albuminuria in patients with type 2 diabetic nephropathy," Journal of the American Society of Nephrology, 2014; 25(5): 1083–1093.
76. Study of Diabetic Nephropathy with Atrasentan (SONAR), http://clinicaltrials.gov/ct2/show/NCT01858532?term=nct01858532&rank=1.
77. Perkovic, V., Jardine, M.J., Neal, B., Bompoint, S., Heerspink, H.J.L., Charytan, D.M., et al., 2019. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. New England Journal of Medicine, 380: 2295e 2306.
78. Preiss, D., Sattar, N., 2019. Research digest: SGLT2 inhibition in kidney and liver disease. Lancet Diabetes Endocrinol, 7: 427.
79. BAsh LD, Selvin E, Steffes M, Coresh J, Astor BC. Poor glycemic control in diabetes and the risk of incident chronic kidney disease even in the absense of albuminuria and retinopathy: Atherosclerosis Risk in Communities (ARIC) study. Arch InternMed, 2008; 168: 2440–2447.
80. Levin SR, Coburn JW, Abraira C, et al.; Veterans Affairs Cooperative Study on Glycemic Control and Complications in Type 2 Diabetes Feasibility Trial Investigators. Effect of intensive glycemic control

on microalbuminuria in type 2 diabetes. Diabetes Care, 2000; 23: 1478–1485.
81. Tanji N, Markowitz GS, Fu C, et al. Expression of advanced glycation end products and their cellular receptor RAGE in diabetic nephropathy and nondiabetic renal disease. J Am Soc Nephrol, 2000; 11: 1656–1666.
82. Degenhardt TP, Alderson NL, Arrington DD, et al. Pyridoxamine inhibits early renal disease and dyslipidemia in the streptozotocin-diabetic rat. Kidney Int., 2002; 61: 939–950.
83. G. Vlotides and P. R. Mertens, "Sodium-glucose cotransport inhibitors: mechanisms, metabolic effects and implications for the treatment of diabetic patients with chronic kidney disease," Nephrology Dialysis Transplantation, 2014.
84. de Nicola, F. B.Gabbai, M. E. Liberti, A. Sagliocca, G. Conte, and R. Minutolo, "Sodium/glucose cotransporter 2 inhibitors and prevention of diabetic nephropathy: targeting the renal tubule in diabetes," American Journal of Kidney Diseases, 2014; 64(1): 16–24.
85. A. M. Brooks and S. M.Thacker, "Dapagliflozin for the treatment of type 2 diabetes," Annals of Pharmacotherapy, 2009; 43: 7-8, 1286–1293.
86. S. Ohga, K. Shikata, K. Yozai et al., "Thiazolidinedione ameliorates renal injury in experimental diabetic rats through anti-inflammatory effects mediated by inhibition of NF-kappaB activation," The American Journal of Physiology—Renal Physiology, 2007; 292(4): F1141–F1150.
87. Z. Zhang, W. Yuan, L. Sun et al., "1,25-dihydroxyvitamin D3 targeting of NF-κB suppresses high glucose-induced MCP-1 expression in mesangial cells," Kidney International, 2007; 72(2): 193–201.
88. Y. Huang, H. Yu, J. Lu et al., "Oral supplementation with cholecalciferol 800 IU ameliorates albuminuria in Chinese type 2 diabetic patients with nephropathy," PLoS ONE, 2012; 7(11): Article ID e50510.
89. S. Bonakdaran, M.Hami, and A.Hatefi, "The effects of calcitrio on albuminuria in patients with type-2 diabetes mellitus.," Saudi Journal of kidney Diseases and Transplantation, 2012; 23(6): 1215–1220.
90. U. Krairittichai, R. Mahannopkul, and S. Bunnag, "An open label, randomized controlled study of oral calcitriol for the treatment of proteinuria in patients with diabetic kidney disease," Journal of the Medical Association of Thailand, 2012; 95, supplement 3: S41–S47.
91. P. Y. Chuang and J. C. He, "JAK/STAT signaling in renal diseases," Kidney International, 2010; 78(3): 231–234.
92. P. M. Garc´ıa-Garc´ıa, M. A. Getino-Meli´an, V. Dom´ınguez- Pimentel, and J. F.Navarro-Gonz´alez, "Inflammation in diabetic kidney disease," World Journal of Diabetes, 2014; 5(4): 431–443.
93. G. Ortiz-Mu˜noz, V. Lopez-Parra, O. Lopez-Franco et al., "Suppressors of cytokine signaling abrogate diabetic nephropathy," Journal of the American Society of Nephrology, 2010; 21(5): 763–772.
94. A Study to Test Safety and Efficacy of Baricitinib in Participants with Diabetic Kidney Disease, https://clinicaltrials.gov/ show/NCT01683409.
95. K. Fallahzadeh, B. Dormanesh, M.M. Sagheb et al., "Effect of addition of silymarin to renin-angiotensin systeminhibitors on proteinuria in type 2 diabetic patients with overt nephropathy: randomized, double-blind, placebo-controlled trial," American Journal of Kidney Diseases, 2012; 60(6): 896–903.
96. J. Gaedeke, N. A. Noble, and W. A. Border, "Curcumin blocks multiple sites of the TGF-β signaling cascade in renal cells," Kidney International, 2004; 66(1): 112–120.
97. Y. S. Kim, Y. Ahn, M. H. Hong et al., "Curcumin attenuates inflammatory responses of TNF-α-stimulated human endothelial cells," Journal of Cardiovascular Pharmacology, 2007; 50(1): 41–49.
98. P. Khajehdehi, M. Pakfetrat, K. Javidnia et al., "Oral supplementation of turmeric attenuates proteinuria, transforming growth factor-β and interleukin-8 levels in patients with overt type 2 diabetic nephropathy: a randomized, double-blind and placebo-controlled study," Scandinavian Journal of Urology and Nephrology, 2011; 45(5): 365–370.