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Review Article

# TREATMENT OF DIABETIC NEPHROPATHY: A REVIEW

Dr. Niyamtullah Musalman[1*], Prof. Dr. Lizun Jin[2], Dr. Laxmi Narayan Goit[3] and Dr. Sandeep Roy[4]

*[1, 3]Department of Cardiology, the first affiliated Hospital of Yangtze University, Jingzhou, Hubei, P.R China*

*[2]Department of Cardiology, clinical college of Yangtze University and the first affiliated hospital to Yangtze University, Jingzhou, Hubei, P.R china*

*[4]Department of Cardiology, the Second affiliated Hospital of Yangtze University, Jingzhou, Hubei, P.R China*

## ABSTRACT

Diabetic nephropathy (DN) is a dreaded consequence of diabetes mellitus, accounting for about 40% of end-stage renal disease (ESRD). It is responsible for significant morbidity and mortality, both directly by causing ESRD and indirectly by increasing cardiovascular risk. Extensive research in this field has thrown light on multiple pathways that can be pharmacologically targeted, to control or reverse the process of DN. Glomerulocentric approach of DN still continues to produce favorable results as evidenced by the recent data on SGLT-2(sodium glucose co-transporter type 2) inhibitors. Beyond the glomerular mechanisms, numerous novel pathways have been discovered in the last decade. Some of these pathways target inflammatory and oxidative damage, while the others target more specific mechanisms such as AGE-RAGE (advanced glycation end products-receptors for advanced glycation end products), ASK (apoptotic signal-regulating kinase), and endothelin-associated pathways. As a result of the research, a handful of clinically relevant drugs have made it to the human trials which have been elucidated in the following review, bearing in the mind that there are many more to come over the next few years. Ongoing research is expected to inform the clinicians regarding the use of the newer drugs in DN.

**Keywords:** Diabetic Mellitus, End stage renal disease, Proteinuria, Hyperglycemia and overt nephropathy

## INTRODUCTION

Diabetes mellitus is a major cause of morbidity and mortality around the entire world [1]. Kidney disease secondary to diabetes mellitus, termed as diabetic nephropathy (DN), accounts for over 40% of end stage renal disease (ESRD). It is also a strong predictor of cardiovascular disease and associated mortality. Among the patients with type 1 diabetes, the prevalence of DN is about 40%. Ten years after the diagnosis of type-2 diabetes, about 25 % patients have DN [2]. Worldwide prevalence of diabetes is rapidly increasing, making it one of the most significant contributors to healthcare costs. DN to progress through five stages based on the changes in glomerular filtration rate and urinary albumin excretion. It starts as glomerular hyper filtration due to hyperglycemias. Next is the silent stage. This stage is characterized by histological abnormalities without clinical disease. The third stage is the incipient nephropathy stage involving urinary albumin losses (30-300 mg/day) and the fourth stage is characterized by overt proteinuria (>300 mg/day). The fifth stage is end-stage kidney disease requiring renal replacement therapy (Table 1).

Initial stages of DN are characterized by microalbuminuria, which progresses to overt proteinuria over time. Proteinuria appears to be both the cause and the effect of DN [3]. For over two decades, RAAS (renin Angiotensin aldosterone system) blockade has played an important role in delaying the progression of DN via anti-hypertensive and anti-proteinuria effects. However, there is emerging evidence on newer drugs that could mitigate deleterious effects of diabetes on renal function. DN has been an extremely active area of pharmacological research in the last decade, and multiple drugs targeting various pathways have been studied with only a few encouraging results [4]. This review attempts to summarize some of the newer and clinically significant pharmacotherapy.

| **Stage of Diabetic nephropathy** | |
|---|---|
| 1 | Glomerular hyperfiltration |
| 2 | Silent stage |
| 3 | Incipient nephropathy. |
| 4 | Overt nephropathy |
| 5 | End stage kidney disease |

**Table 1:** Stage of Diabetic Nephropathy

## Pathogenesis of DN:

Pathogenesis of DN is a complex and multi factorial process that appears to be a combination of inflammation, oxidative stress, and epigenetic factors [5]. However, the role of glomerular hyper filtration early in the course of diabetes lies at the heart of pathophysiology of DN. single-nephron GFR studies showed that the deregulated tubuloglomerular feedback (TGF) in diabetic rats leads to a reduced tone in afferent arteriole which causes glomerular hypertension. Through these experiments, we currently understand that (a) juxtaglomerular apparatus fine-tunes the glomerular filtration and is an important homeostatic mechanism that regulates glomerular pressures; (b) adenosine is an important mediator of TGF; and (c) in diabetes, the activity of sodium-glucose transporter (SGLT-2) is increased, leading to an enhanced absorption of sodium in

the proximal convoluted tubule. These results in a decreased distal delivery of sodium, which in turn signals TGF mechanism to decrease the afferent arteriolar tone. Ultimately, this leads to glomerular hyperfiltration, thus beginning the pathologic changes of DN.

The mechanism of decreased distal sodium delivery leading to glomerular hyperfiltration was confirmed by the phenomenon called "salt paradox". In this phenomenon, when rats in early phases of diabetes were salt restricted, they absorbed most of the sodium in the proximal convoluted tubule that lowered the delivery of sodium to the distal convoluted tubule. This decreased local adenosine levels resulting in the dilation of afferent arteriole.

## Therapies:

## SGLT-2 inhibitors:

Sodium glucose co-transporter-2 inhibitors are a unique class of diabetic agents that have beneficial effects on blood pressures, weight, and arterial stiffness [6]. Empagliflozin, dapagliflozin, and canagliflozin are the Unites States Food and Drug Administration approved agents available in the United States. The renal significance of these drugs comes from their ability to restore a deregulated TGF. Restoration of this mechanism results in reduced glomerular filtration and glomerulomegaly [7]. The enhanced absorption of sodium proximally leads to decreased distal sodium delivery, which results in afferent arteriolar vasodilatation and glomerulomegaly. When used in this scenario, SGLT-2 inhibitors restore TGF by blocking proximal sodium and glucose absorption. This in turn results in reduced glomerular filtration. In EMPA-REG OUTCOME trial (empagliflozin cardiovascular event outcome event trial in type 2 diabetes mellitus (T2DM) patients), the effect of empagliflozinwas studied on cardiac outcomes in patients with T2DM. However, worsening renal end points (defined as progression to macroalbuminuria [UACR to 300mg/gm], doubling of serum creatinine, dialysis, or mortality from renal causes) was one of the secondary outcomes in this study. Out of 7020 subjects studied, 2250 (32%) had chronic kidney disease (CKD) (estimated GFR (eGFR)>60 ml/min and/or UACR >300 mg/gm). Patients were randomized to receive empagliflozin (10 or 25 mg) or placebo along with standard diabetes care. At the end of ~164 weeks, there was a reduction in cardiovascular death, all-cause mortality, and hospitalization in all the study subjects. The risk reduction was similar between patients with and without CKD. Even when the patients were stratified based on the severity of albuminuria (UACR: <30 mg/gm, 30–300 mg/gm and >300 mg/gm), the end-point reduction did not differ significantly.

More importantly, from a renal perspective, renal end points occurred in 12.7% in empagliflozin group versus 18.8% in placebo group. Worsening of albuminuria occurred in 11.2% in treatment group compared to 16.2% in the control group. Doubling of creatinine occurred in 1.5% in the treatment group compared to 2.6% in the control group. All these outcomes reached statistical significance. Despite a better renal outcome in this study, it must be noted that this study was not designed with renal outcomes as primary end point. A larger randomized controlled trial (RCT) targeting renal outcomes is still needed. Canagliflozin, another SGLT-2, was investigated in an integrated study called CANVAS program. This program in turn consisted of two sister programs, CANVAS (canagliflozin cardiovascular) and CANVASR (CANVAS-renal) [8]. CANVAS involved 4330

participants and CANVAS-R involved 5812 participants. At the end of follow-up period, the two arms of the trial were jointly analyzed to study the outcomes. CANVAS was geared primarily towards studying cardiac outcomes, and the renal outcomes were secondary. One of the secondary outcomes was progression of albuminuria. The study subjects were followed for ~3.6 years. Primary outcomes (cardiac death, acute coronary, and stroke) were significantly less in the treatment group compared to the control group. Progression of albuminuria occurred less frequently in the treatment group with a hazard ratio of 0.64. Regression of albuminuria occurred more frequently in the treatment group compared to the control group with a corresponding hazard ratio of 1.7. The composite renal outcome (reduction in eGFR <40%, dialysis, death from kidney failure) occurred less frequently in the canagliflozin group.

In another pooled analysis of 11-phase 3 RCT involving patients with type 2 diabetes, effects of dapagliflozin was analyzed on changes in eGFR and UACRs [9]. In this analysis, there were 220patients with eGFR between 12 and 45 ml/min/1.73m2. At the end 102 weeks of the study period, dapagliflozin 5 mg and 10 mg daily reduced UACR by 47.1% and 38.4 %, respectively. No changes in eGFR were noted at the end of study between the two groups. All the above RCTs established the role of potential nephroprotective ability of SGLT-2 inhibitor seven though none of them were designed to study renal outcomes as primary end points. A dedicated RCT to study the effects of SGLT-2 inhibitors on renal outcomes named CREDENCE trial (canagliflozin and renal events in diabetes with established nephropathy clinical evaluation) is currently in process.

## Incretin-related therapies:

Incretin-related therapies include GLP-1 (glucagon like peptide type 1) analogues and DPP-4 (dipeptidylpeptidase type 4) inhibitors. GLP-1 is a gastrointestinal hormone that enhances insulin secretion and has a pleotropic effect on glucose metabolism. GLP-1 is metabolized and degraded by DPP-4 at proximal convoluted tubules and podocytes [10]. Experiments have shown that insulin resistance in diabetes results from a combination of lower levels of GLP-1 and increased expression of DPP-4.

## GLP-1 agonists:

Exenatide, liraglutide, dulaglutide, and albiglutide are the currently available GLP-1 analogues in the drug market. Some of the uncontrolled studies in type 2 diabetes patients with GLP-1 agonists suggested a trend towards improvement in albuminuria which provided the impetus to study the effects of GLP-1analogues in DN [11]. SCALE diabetes trial, an RCT designed to study the benefit of liraglutide on weight reduction, noted that the drug caused a dose-dependent reduction in albuminuria. In another integrated analysis that included nine clinical trials, dulaglutide caused reduction of albuminuria compared to placebo, long-acting glargine insulin, and other diabetic medications. In this study, dulaglutide lowered UACR by 17% compared to placebo which reduced UACR by only 10 %. Similarly, dulaglutide reduced UACR by 16.7% compared to glargine, which reduced UACR by only 3.7%. Reduction of albuminuria was statistically significant in both cases. However, there were no significant changes in eGFR over the follow-up period (26–104 weeks). In another small RCT involving 42 patients, Exenatide showed a statistically significant reduction in 24-h urine albumin, urinary TGF-beta1 (transforming growth factor), and type 4 collagen compared toglimepiride [12]. Two RCTs, LEADER and

SUSTAIN-6 were designed to study liraglutide and Semaglutide, respectively, on cardiac end points in type 2 diabetes. They also included pre-specified composite microvascular outcomes such as worsening of new-onset proteinuria, doubling of serum creatinine, or need for dialysis. However, renal outcomes were secondary again. Lower rate of renal outcomes were noted in both LEADER trial and SUSTAIN-6 trial. In conclusion, most studies involving GLP-1 analogues show a favorable effect on albuminuria, although none of these trials studied renal end points as primary outcomes. Large RCTs targeting GLP-1effects on pre-specified primary renal outcomes are required to enhance our understanding regarding the effects of this drug class on DN.

## DPP-4 inhibitors:

Among the available DPP-4 inhibitors (linagliptin, saxagliptin, alogliptin, and Sitagliptin), linagliptin has been extensively analyzed with regard to DN. LIRA-RENAL RCT was primarily designed to study the effect of liraglutide in lowering glycohaemoglobin in patients with moderate renal impairment(eGFR 30–59 ml/min/1.73m2). At the end of26 weeks, albuminuria in linagliptin group was 17 % lower, although it did not attain statistical significance [13]. MARLINA-T2D trial was designed to investigate linagliptin in patients with T2DM and CKD [14].This study, which involved 360 participants who were followed over 24 weeks, was also designed to test superiority of linagliptin over placebo in terms of albuminuria. Despite a trend towards reduction in albuminuria, the differences between the study groups were not statistically significant. In a pooled analysis of 13 phase 2 or 3 RCTs; the effect of linagliptin was studied on renal end points. Primary end points in this study were new onset of moderate albuminuria (UACR > 30−300 mg/gm), new onset of severe elevation in albuminuria (UACR increased to >300 mg/gm from lower values), reduction in kidney function from a baseline value, and halving of eGFR and acute kidney injury (AKI) incidence. Out of 5466 participants, 3505 received linagliptin and the rest received placebo. In this analysis, linagliptin significantly reduced the hazard of the first occurrence of primary event by 16%. New-onset moderate elevation in albuminuria was reduced by 18%. No difference in decline in eGFR was noted between the two groups.

In SAVOR-TIMI trial, a large RCT with 16,492 participants, the effect of saxagliptin was studied on cardiovascular outcomes with patients of type 2 diabetes. In this study, saxagliptin did not improve cardiovascular outcomes at the end of follow-up period (2.1 years). However, the data was re-analyzed for albuminuria. It was noted that irrespective of baseline UACR, treatment with saxagliptin was associated with improvement of albuminuria for normoalbuminuria, microalbuminuria, and macroalbuminuria.

DPP-4 inhibitors, like GLP1 agonists, do appear to have a beneficial effect on albuminuria but none of the RCTs above were designed or powered to detect renal outcomes as primary. At this point, the RCT called CARMELINA trial (composite and renal microvascular outcome study with linagliptin) has recruited 7003 participants to study composite renal end points over 54 months. The results are much awaited.

## Endothelin receptor antagonists:

Data from both human and animal studies suggest that albuminuria is not only a marker of renal disease but also contributes to the progression of kidney disease. There is emerging evidence of role of endothelin in the pathogenesis of proteinuria [15]. In addition to this, endothelin also plays a role in the up

regulation of inflammation and fibrosis in renal parenchyma [16]. Therefore, endothelin antagonists were hypothesized to improve albuminuria addition to causing anti-inflammatory and anti-fibrotic effects. ASCEND, a multicentre RCT, was designed to study the effects of avosentan, an endothelin antagonist, on composite renal outcomes including albuminuria. 1392 subjects were randomized to receive placebo and avosentan 25 mg or 50 mg. The subjects were already on RAAS blockade for the management of DN. Unfortunately, this study had to be terminated prematurely after 4 months due to excessive number of cardiovascular deaths in the avosentan group. However, the treatment group did experience significant reduction of albuminuria. Median reduction of albuminuria was 44.3, 49.3, and 9.7%, respectively, in 25 mg, 50 mg, and placebo groups. Congestive heart failure and fluid retention were the notable adverse effects.

Atrasentan, a highly selective ET-A antagonist, was studied next. Fluid retention was thought to be mediated mainly via ET-B receptor and Atrasentan showed less of these side effects in animal models [17]. 211 participants were randomized to receive Atrasentan 0.75 mg/day, 1.25 mg/day, or placebo and followed for 12 weeks. Compared to placebo, both doses of Atrasentan caused at least 35% reduction in UACR. Estimated GFR changes between the groups were not significant. Fluid retention was not noted in the low-dose group, but Atrasentan 1.25 mg/day significantly increased the body weight compared to placebo. Encouraged by this trial, a larger trial was planned.

## Mineralocorticoid receptor antagonists (MRA):

Apart from regulating sodium absorption and potassium excretion in the kidney, mineralocorticoid receptor activation is associated with activation of pro-inflammatory, oxidative, and pro-fibrotic pathways in various organ systems [18]. Therefore, the antagonism of mineralocorticoid receptors results in anti-inflammatory, antioxidative, and anti-fibrotic effects. However, steroidal MRAs such as eplerenone and spironolactone, when added to ACE-I or ARB, often result in severe Hyperkalemia. Finerenone, a novel nonsteroidal MRA, despite having more selectivity towards mineralocorticoid receptors, caused lower incidence of Hyperkalemia in earlier trials [19]. Lower incidence of Hyperkalemia by finerenone is due to its characteristic tissue distribution. Older MRAs cause more Hyperkalemia by accumulating three- to six fold higher in kidney when compared to newer drugs such as finerenone. ARTS-DN was a randomized trial designed to test the efficacy and safety of finerenone in patients with DN and persistent albuminuria. Participants in this study received oral finerenone 1.25, 2.5, 5, 7.5, 10, 15 and 25 mg/day or placebo. Eight hundred and twenty one patients were randomized and followed for 90 days. Primary outcome was the ratio of UACR at 90 days versus baseline. At the end of the study, the finerenone group had dose-dependent reduction in UACR from the dose of 7.5 mg/day and above.

Hyperkalemia was noted in 1.8 % of the intervention group and 0% in placebo group. However, eGFR changes did not reach statistical significance in the treatment compared to placebo group [20]. Although this trial determined the effective dose of finerenone, head-to-head comparison with other MRA is needed to study its superiority with respect to changes in albuminuria and Hyperkalemia.

## Phosphodiesterase inhibitors:

Inflammation is believed to play a key role in progression on DN. Pentoxifylline, a nonspecific Phosphodiesterase inhibitor, is known for its anti-inflammatory and anti-fibrotic properties in experimental models [21]. PREDIAN trial was designed to test if Pentoxifylline would benefit patients with DN. In this study, 169 patients with eGFR < 60 ml/min/1.73 m2 were optimized on RAAS blockers and randomized to receive Pentoxifylline or placebo. Study subjects were followed for duration of ~1 year [22]. At the end of the study period, eGFR in the treatment group decreased by 2 ml/min/1.73m2 compared to 6.5 ml/min/1.73m2 in the control group. This study therefore concluded by saying that Pentoxifylline could slow the progression of DN in advanced CKD. However, there were two major drawbacks limiting the generalizability of this trial.

## Xanthine oxidase inhibitors:

Prospective data are available to implicate uric acid levels as a risk factor in rapid decline of eGFR and development of macroalbuminuria in type 2 diabetes. Multiple cohort studies suggest that elevated uric acid levels are associated with faster progression of diabetic kidney disease [23]. It was therefore hypothesized that lowering serum uric acid levels can slow the progression of DN. In fact, a smaller randomized trial involving 113 participants showed that allopurinol use may slow the decline in eGFR in DN. Encouraged by the literature and smaller trials, a large RCT, is currently testing allopurinol type 1 diabetic patients to see if this drug slows the progression of renal disease [24].

## Drugs targeting AGE-RAGE axis:

Diabetes mellitus leads to glycosylation and oxidation of proteins, lipids, and various cell surface receptors, leading to the formation of advanced glycosylation end products (AGEs). Several receptors for AGE have been identified which are named RAGE (receptors for AGE). These receptors initiate maladaptive changes by initiating certain intracellular pathways, which disrupt cellular function. Advanced glycationend products-receptors for advanced glycation end products (AGE-RAGE) axis is now recognized to be an important pathway through which diabetes contributes to vascular damage [25].

Pyridoxamine dihydrochloride, a derivative of vitamin B6, is known to inhibit a broad range of Mechanisms that is responsible for the formation of AGEs [26]. In a pilot trial (PYR-210), Pyridoxamine showed a trend towards improved creatinine in a cohort of patients with DN. Proteinuria differences did not reach statistical significance. However, the pilot was not powered to detect changes in proteinuria.

## Antioxidants:

Oxidative stress has been proposed as an important mechanism in progression of renal disease. There is emerging evidence to support that reactive oxygen species cause impaired activity of the transcription factor call Nrf-2 (nuclear 1 factor-related factor 2) [27]. A synthetic triterpenoid derivative, bardoxolone methyl, is a potent activator of Nrf-2 that was shown to reduce oxidative stress in rat models [28]. BEAM study, a RCT, was designed to study the effect of bardoxolone on CKD patients. In this RCT, 227 patients with CKD (eGFR 20–45 ml/min/1.73m2) were assigned to receive 25, 75, or 150 mg of bardoxolone daily versus placebo. At the

end of study that lasted 52 weeks, eGFR in the treatment group was significantly higher compared to the placebo group. Encouraged by the results, another larger RCT, BEACON, was designed to test bardoxolone in 2185 patients with type-2 diabetes and stage 4 CKD [29]. Unfortunately, the study was prematurely terminated after 9 months due to higher rate of cardiovascular deaths. Another oxidative stress pathway mediated by activation of apoptotic signal-regulating kinase-1(ASK-1) has received attention recently. ASK-1 pathway activation results in downstream activation of terminal kinase, leading to the production of inflammatory chemokines. A novel molecule GS-4997 was shown to reduce inflammation in rat models by inhibiting ASK-1 pathway. Currently, an RCT is in process to test this drug in DN with stage 3 and 4 CKD. The primary outcome being studied is change in eGFR and the secondary outcome is change in albuminuria [30].

## CONCLUSION

DN remains a very active field of research with multiple drugs in the research pipeline in both human and animal studies. SGLT-2 inhibitors currently offer more promise than most other drugs under active investigation. This class of drugs is followed by Incretin-related therapies which might prove beneficial in management of DN. However, more research and RCTs are needed to support their use in delaying the progression of DN. Strict blood pressure and glycemic control along with RAAS blockade still remain the standard of care to delay the progression to ESRD. Ongoing research is expected to inform the clinicians regarding the use of the newer drugs in DN.

## Abbreviations:

CHD: Coronary heart disease.

HF: Heart failure.

CV: Cardiovascular.

DM: Diabetes mellitus.

CKD: Chronic kidney disease

## REFERENCES

1. Roglic, G., et al., *The burden of mortality attributable to diabetes: realistic estimates for the year 2000.* Diabetes Care, 2005. **28**(9): p. 2130-5.
2. Adler, A.I., et al., *Development and progression of nephropathy in type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS 64).* Kidney Int, 2003. **63**(1): p. 225-32.
3. Tabaei, B.P., et al., *Does microalbuminuria predict diabetic nephropathy?* Diabetes Care, 2001. **24**(9): p. 1560-6.
4. Mann, J.F., et al., *Avosentan for overt diabetic nephropathy.* J Am Soc Nephrol, 2010. **21**(3): p. 527-35.
5. Nguyen, D.V., L.C. Shaw, and M.B. Grant, *Inflammation in the pathogenesis of microvascular complications in diabetes.* Front Endocrinol (Lausanne), 2012. **3**: p. 170.

6. Stanton, R.C., *Sodium glucose transport 2 (SGLT2) inhibition decreases glomerular hyperfiltration: is there a role for SGLT2 inhibitors in diabetic kidney disease?* Circulation, 2014. **129**(5): p. 542-4.
7. Cherney, D.Z., et al., *Renal hemodynamic effect of sodium-glucose cotransporter 2 inhibition in patients with type 1 diabetes mellitus.* Circulation, 2014. **129**(5): p. 587-97.
8. Neal, B., V. Perkovic, and D.R. Matthews, *Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes.* N Engl J Med, 2017. **377**(21): p. 2099.
9. Dekkers, C.C.J., et al., *Effects of the sodium-glucose co-transporter 2 inhibitor dapagliflozin in patients with type 2 diabetes and Stages 3b-4 chronic kidney disease.* Nephrol Dial Transplant, 2018. **33**(7): p. 1280.
10. Tonneijck, L., et al., *Incretin-based drugs and renoprotection-is hyperfiltration key?* Kidney Int, 2015. **87**(3): p. 660-1.
11. Imamura, S., K. Hirai, and A. Hirai, *The glucagon-like peptide-1 receptor agonist, liraglutide, attenuates the progression of overt diabetic nephropathy in type 2 diabetic patients.* Tohoku J Exp Med, 2013. **231**(1): p. 57-61.
12. Zhang, H., et al., *Exenatide reduces urinary transforming growth factor-beta1 and type IV collagen excretion in patients with type 2 diabetes and microalbuminuria.* Kidney Blood Press Res, 2012. **35**(6): p. 483-8.
13. Davies, M.J., et al., *Efficacy and Safety of Liraglutide Versus Placebo as Add-on to Glucose-Lowering Therapy in Patients With Type 2 Diabetes and Moderate Renal Impairment (LIRA-RENAL): A Randomized Clinical Trial.* Diabetes Care, 2016. **39**(2): p. 222-30.
14. Groop, P.H., et al., *Linagliptin and its effects on hyperglycaemia and albuminuria in patients with type 2 diabetes and renal dysfunction: the randomized MARLINA-T2D trial.* Diabetes Obes Metab, 2017. **19**(11): p. 1610-1619.
15. Hocher, B., et al., *Effects of endothelin receptor antagonists on the progression of diabetic nephropathy.* Nephron, 2001. **87**(2): p. 161-9.
16. Simonson, M.S. and F. Ismail-Beigi, *Endothelin-1 increases collagen accumulation in renal mesangial cells by stimulating a chemokine and cytokine autocrine signaling loop.* J Biol Chem, 2011. **286**(13): p. 11003-8.
17. Opgenorth, T.J., et al., *Pharmacological characterization of A-127722: an orally active and highly potent ETA-selective receptor antagonist.* J Pharmacol Exp Ther, 1996. **276**(2): p. 473-81.
18. Haller, H., et al., *Finerenone: a New Mineralocorticoid Receptor Antagonist Without Hyperkalemia: an Opportunity in Patients with CKD?* Curr Hypertens Rep, 2016. **18**(5): p. 41.
19. Barfacker, L., et al., *Discovery of BAY 94-8862: a nonsteroidal antagonist of the mineralocorticoid receptor for the treatment of cardiorenal diseases.* ChemMedChem, 2012. **7**(8): p. 1385-403.
20. Bakris, G.L., et al., *Effect of Finerenone on Albuminuria in Patients With Diabetic Nephropathy: A Randomized Clinical Trial.* Jama, 2015. **314**(9): p. 884-94.
21. Strutz, F., et al., *Effects of pentoxifylline, pentifylline and gamma-interferon on proliferation, differentiation, and matrix synthesis of human renal fibroblasts.* Nephrol Dial Transplant, 2000. **15**(10): p. 1535-46.

22. Navarro-Gonzalez, J.F., 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**(1): p. 220-9.
23. Zoppini, G., et al., *Serum uric acid levels and incident chronic kidney disease in patients with type 2 diabetes and preserved kidney function.* Diabetes Care, 2012. **35**(1): p. 99-104.
24. Maahs, D.M., et al., *Uric acid lowering to prevent kidney function loss in diabetes: the preventing early renal function loss (PERL) allopurinol study.* Curr Diab Rep, 2013. **13**(4): p. 550-9.
25. Goldin, A., et al., *Advanced glycation end products: sparking the development of diabetic vascular injury.* Circulation, 2006. **114**(6): p. 597-605.
26. Chetyrkin, S.V., et al., *Pyridoxamine protects proteins from functional damage by 3-deoxyglucosone: mechanism of action of pyridoxamine.* Biochemistry, 2008. **47**(3): p. 997-1006.
27. Ruiz, S., et al., *Targeting the transcription factor Nrf2 to ameliorate oxidative stress and inflammation in chronic kidney disease.* Kidney Int, 2013. **83**(6): p. 1029-41.
28. Yates, M.S., et al., *Pharmacodynamic characterization of chemopreventive triterpenoids as exceptionally potent inducers of Nrf2-regulated genes.* Mol Cancer Ther, 2007. **6**(1): p. 154-62.
29. de Zeeuw, D., et al., *Bardoxolone methyl in type 2 diabetes and stage 4 chronic kidney disease.* N Engl J Med, 2013. **369**(26): p. 2492-503.
30. Lin, J.H., et al., *Design of a phase 2 clinical trial of an ASK1 inhibitor, GS-4997, in patients with diabetic kidney disease.* Nephron, 2015. **129**(1): p. 29-33.