THE PROTECTIVE ROLE OF THE DIPEPTIDYL PEPTIDASE-4 INHIBITOR, LINAGLIPTIN IN ACUTE AND CHRONIC KIDNEY INJURY CONDITIONS

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ABSTRACT

The dipeptidyl peptidase inhibitors (DPP-4) are a class of anti-diabetics approved for the oral treatment of type 2 diabetes mellitus (DM). That act by preventing the degradation of incretin hormones: which play an important role in insulin secretion and blood glucose regulation. The DPP-4 inhibitors have the potential to offer beneficial effects beyond the improvement of glycemic control which lies with the functional ability of the DPP-4 enzyme to cleave a variety of peptides other than incretins that have established renal and cardiovascular effects. Linagliptin (Lina) is distinctive amongst gliptins because it is the only compound that can be eliminated via a non-renal pathway, so a reduction in the glomerular filtration rate doesn't require dose adjustment. In addition, Lina is the only identified DPP-4 inhibitor that has been evaluated in a multicenter randomized clinical trial designed to thoroughly evaluate cardio-renal outcomes in patients with type 2 DM. This review provides a brief overview of the current literature on the renoprotective effects of Lina in experimental models of acute and chronic kidney disease (CKD) and clinical studies and sheds some light on the underlying mechanisms of protection.

Keywords: Acute kidney injury; Chronic kidney disease; DPP-4 Inhibitors; Linagliptin; Renal fibrosis.

Introduction

The major function of the kidney is to remove toxic by-products of metabolism from the blood to produce urine. It also performs various vital functions in the body including electrolyte balance and blood pH homeostasis, regulation of blood pressure, erythropoiesis, and vitamin D metabolism in addition to detoxification and excretion of toxic metabolites and drugs **(Bajaj *et al.* 2018)**. Because of its high workload, the kidney is an energy-demanding organ that is constantly exposed to endogenous and exogenous insults, leading to the development of either acute kidney injury (AKI) or CKD **(Kamt *et al.* 2023)**. According to Kidney Disease Improving Global Outcomes, AKI is defined as a sudden and often reversible decline in renal function, and this is indicated by increased serum creatinine level or decreased urinary output that lasts 7 days or more **(Makris and Spanou 2016)**. Approximately 12-13 million cases of AKI are reported each year. The global prevalence of AKI-associated mortality is approximately 1.7 million deaths per year. Sepsis, ischemia/reperfusion injury (IRI), and nephrotoxins are some of the factors that can cause AKI **(Dagar *et al.* 2023)**. There is evidence that other biomarkers may be more sensitive and may be elevated earlier in the course of AKI compared to creatinine which can be measured in the plasma and urine such as neutrophil gelatinase-associated lipocalin, kidney injury molecule-1, and cystatin C **(Wen and Parikh 2021)**. Persistent or repeated AKI and severe cases are associated with a higher risk for progression to CKD, a condition that affects 8-15% of the global population and is characterized by a progressive loss of renal function or estimated glomerular filtration rate (GFR) <60 mL/min/1.73 m^2 lasting >3 months or longer with accompanying kidney tissue damage (such as glomerulosclerosis and tubular injuries) and results in end-stage kidney disease (ESKD) or complete kidney failure. This devastating disorder requires dialysis or life-saving kidney transplantation. Diabetic nephropathy (DN) and DM as well as hypertension appear to be the most frequent causes of CKD **(Mima 2023)**. The development and progression of CKD are also associated with the presence of chronic inflammation, oxidative stress, and ischemia **(Gluba-Sagr *et al.* 2023)**. The tubulo-interstitial fibrosis is considered to be the final common pathway in the evolution of virtually all types of CKD, regardless of the primary origin of renal injury **(Li *et al.* 2022)**. Characteristic features of renal fibrosis involve the deposition of extracellular matrix (ECM) proteins in tubular and interstitial regions **(Bülow and Boor 2019)**. Moreover, epithelial-mesenchymal transition (EMT) has been suggested to contribute to renal interstitial fibrosis as a result of enhanced expression of vimentin, fibronectin, and α-SMA, as well as reduced levels of E-cadherin in kidney epithelial cells **(Li *et al.* 2019)**. Currently, there are no pharmaceutical products to cure AKI or CKD. As a result, slowing or stopping the advancement of such devastating diseases has arisen as a critical issue for the global health community. To fight kidney diseases, numerous therapeutic approaches have been explored (**Kamt *et al.* 2023**). In this review article, we will focus on studies using animal and *in vitro* models to explore the protective effects of Lina on kidney injuries and some clinical studies and elucidate the underlying mechanisms.

1. DPP-4 enzyme

The DPP-4 (also known as CD26) is a multifunctional glycoprotein with serine exopeptidase activity that is highly expressed in renal endothelial and proximal tubular cells. It is not only just an enzyme with protease activity but it also interacts with the ECM, and regulates intracellular signal transduction coupled to the control of cell migration and proliferation (**Shi et *al.* 2016**). There are about 30 peptides that have been identified as substrates for DPP-4, including glucagon like peptide-1 (GLP-1), glucose-dependent insulinotropic peptide, brain natriuretic peptide, neuropeptide Y, high mobility group protein 1 and stromal cell-derived factor 1 (SDF-1) **(Daza-Arnedo *et al.* 2021)**.

The DPP-4 exists in two forms. The first form is the membrane-bound anchored to a lipid bilayer by a single hydrophobic segment located at the N-terminus and has a short cytoplasmic tail of six amino acids. It is found in the membrane of several cell types, including endothelial cells, and T cells, and is strongly up-regulated in activated lymphocytes and kidney tubular cells (located in the membrane brush border of the proximal convoluted tubule in podocytes). The extracellular portion of membrane DPP-4 contains a glycosylation domain, a cysteine-rich domain, and a catalytic domain at the C-terminus **(Shi *et al.* 2016)**. The second isoform is the soluble DPP-4 (sDPP4) which is circulating in the plasma and lacks the intracellular tail and transmembrane regions. In addition, it is responsible for the cleavage of GLP-1, activation of intracellular signaling pathways, and increased proliferation of human lymphocytes, independent of its catalytic activity **(Figure 1)**. The sDPP4 isoform is of great interest in terms of the pleiotropic action of DPP-4 inhibitors **(Ohm *et al.* 2023)**.

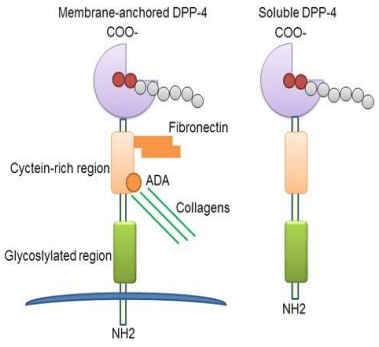

Fig.1 Structure of the DPP-4 enzyme (**Kanasaki 2018)**

1.1. Emerging role of DPP-4 in fibrosis progression

Several studies have shown that the inhibition of DPP-4 significantly reduces TGF-β-induced fibroblast activation and collagen release. **Shi *et al.* (2015)** have reported that TGF-β2 induces TGF-β receptor1/2 (TGF-βR1/2) heterodimer formation, which was attenuated by DPP-4 siRNA in transfected human microvascular endothelial cells. Additionally, **Lee *et al.* (2020)** discovered a role for sDPP4 in modulating the Smad

pathway *via* protease-activated receptor 2 as they detected an increase in phosphorylated Smad2/3 and activation of NF-κB pathway in murine fibroblasts upon stimulation with sDPP4 alone while treatment with Lina prevents fibrotic gene expression patterns, Smad phosphorylation and NF-κB activation. Moreover, the DPP-4 has been identified as a marker of a highly activated subset of myofibroblasts, and its inhibition results in reduced ECM deposition in cultured fibroblasts (**Soare *et al.* 2020**). Furthermore, DPP-4 has been shown to bind to the ECM components collagen 1 and fibronectin, thereby promoting cell migration and forming the architecture of the fibrotic microenvironment. DPP-4 also assists in the degradation of ECM proteins, which further facilitates cell invasion to the site of injury **(Ohm *et al.* 2023)**.

There is accumulating evidence for DPP-4 modulating EMT induction in a variety of different disease models, and DPP-4 inhibition is often associated with a reduction of EMT. In a murine model of diabetic kidney injury, DPP-4 inhibition effectively blocks the up-regulation of EMT transcription factors and restores epithelial markers while reducing interstitial fibrotic changes **(Takagaki *et al.* 2019)**. Other authors suggest that EMT reduction upon DPP-4 inhibition is mediated by the sustained presence of SDF-1/ CXC-motif chemokine ligand 12 modulating TGF-β signaling *via* inhibition of reactive oxygen species (ROS) generation and ERK phosphorylation **(Chang *et al.* 2017)**.

2. Linagliptin

Lina is a DPP-4 inhibitor with a xanthine-based structure. The Lina inhibits DPP-4 activity *in vitro* with an IC_{50} value of 1 nM, demonstrating the highest potency compared to other DDP-4 inhibitors. Additionally, a comparative analysis of binding kinetics of the globally marketed DPP-4 inhibitors (including sitagliptin, saxagliptin, Lina, and alogliptin) found that Lina had the highest binding affinity for DPP-4, one of the fastest binding rates, and the slowest dissociation rate among the former DDP-4 inhibitors **(Schnapp *et al.* 2016)**. The effects of Lina on the kidneys are especially interesting since, depending on its pharmacokinetic properties, it is the only drug that is not eliminated by the kidneys and, thus, does not require dose adjustment in patients with CKD, a consequence of its high level of protein binding and thus low concentration of the free drug. Another intra-class difference in pharmacokinetics is the large volume of distribution of Lina compared with other DPP-4 inhibitors, indicating greater tissue penetration **(Kanasaki 2018)**. The ability of Lina to penetrate deep into kidney tissue has been demonstrated in an *in vivo* study of the tissue distribution of Lina in wild-type and DPP-4-deficient rats using whole-body autoradiography and measurement of tissue radioactivity following administration of the radiolabeled compound, the highest drug concentrations were located in the kidneys and liver **(Fuchs *et al.* 2009)**. A follow-up study employing high-resolution autoradiography found that Lina in the kidney was located mainly on glomerular podocytes and the brush border microvilli of the proximal tubules, with a similar distribution pattern to that of DPP-4 itself **(Greischel *et al.* 2010)**. These data suggest that Lina can reach all DPP-4-containing compartments of the kidney.

3. Protective roles of Lina in kidney injury

Kidney disorders can be induced by several insults, such as diabetes, ischemic reperfusion, drug toxicity, contrast media, and hypertension. If not controlled, AKI can lead to renal failure with a 20% mortality rate (**Duann and Lin 2017**). Lina prophylaxis has been shown to decrease renal structural damage (tubular injury scores), urinary damage markers (serum creatinine), and increase GFR **(Kamt *et al.* 2023)**.

3.1. Diabetic nephropathy

The DN also known as diabetic kidney disease (DKD) is a microvascular complication from type 1 or type 2 DM. It is a major cause of CKD and ESKD. The DN is characterized by a decrease in GFR, proteinuria, and renal fibrosis as well as mitochondrial dysfunction (**Kamt *et al.* 2023**). The effect of Lina on microalbuminuria in patients with DN was investigated in a randomized, double-blinded clinical trial where the percentage of improvement in microalbuminuria in the Lina group was significantly higher than that of the control group during 24 weeks of intervention **(Karimifar *et al.* 2023)**. Additionally, in the study of **Liu *et al.* (2022)** Lina combined treatment with irbesartan showed a favorable clinical efficacy in treating patients with DN as it effectively protects the kidneys and improves kidney function by inhibiting inflammatory and oxidative stress responses. The animal model of **Fujita *et al.* (2022)** showed that the dual inhibition of SGLT2 and DPP-4 with empagliflozin plus Lina treatment promotes natriuresis and improves glomerular hemodynamic abnormalities in KK/Ta-Ins2^{Akita} mice with progressive DKD which was described by a marked reduction in albumin filtration and GFR along with a higher urinary excretion of sodium and adenosine and a significant reduction in urinary excretion levels of prostaglandin E2.

3.2. Contrast-induced AKI (CI-AKI)

CI-AKI is a condition in which a progressive deterioration of kidney function is observed a few days after contrast administration described as an increase in serum creatinine ≥ 0.3 mg/dl or ≥1.5-1.9 times above normal in the 48-72h following contrast medium administration. The nephrotoxic effect is demonstrated by tubular epithelial cell damage and activation of vasoactive molecules which results in oxidative stress, inflammation, ischemic injury, and endothelial cell apoptosis leading to GFR reduction **(Markowska *et al.* 2023).**

The renoprotective effect of Lina against CI-AKI was evaluated in a multicenter prospective randomized controlled study in which patients with DKD were randomly allocated to four equal groups that received Lina and allopurinol either alone or in combination for 2 days before and after radiocontrast. The primary endpoint was the development of post-contrast AKI, defined as a decrease of GFR by or greater than 30% relative to baseline or an increase in serum creatinine that is greater than 0.3 mg/dl relative to baseline or 30% over baseline 72 h after the administration of the contrast. The study

results showed that neither Lina nor allopurinol was superior to the control group (N-acetyl cysteine and saline). However, the combination of the two drugs provided statistically significant renal protection against post-contrast AKI, and none of the post-contrast AKI cases required dialysis **(Fayed *et al.* 2023)**.

3.3. Acute renal ischemia-reperfusion injury

Renal IRI is commonly seen in a variety of clinical settings, including percutaneous coronary intervention, renal transplantation, shock, and embolic diseases. Ischemia occurs when there is a decrease in blood perfusion and the blood flow to organs is reduced this is due to many causes, such as thrombi, trauma, and atherosclerosis and to prevent tissue damage and necrosis, ischemia is resolved by reperfusion. Although ischemic reperfusion is essential to prevent tissue necrosis, it can also cause inflammation and an increase in ROS and reactive nitrogen species **(Tang *et al.* 2023)**. The protective effect of Lina was compared to other structurally unrelated DPP-4 inhibitors (vildagliptin and sitagliptin) in the rat model of renal IRI, where the study results showed that all tested DPP-4 inhibitors did not either reduce increased plasma cystatin C levels, a marker of glomerular function, or altered IRI-related increased renal cytokine expression (CCL2, IL-1β, IL-6, TNF-α) but ameliorated against tubular cell necrosis with varying degrees of drug-specific efficacies. In addition, the renal osteopontin expression, a marker of tubular damage was reduced by all DPP-4 inhibitors **(Reichetzeder *et al.* 2017)**

3.4. 5/6 Nephrectomy

The rat remnant kidney model has been one of the most valuable and extensively investigated experimental non-diabetic CKD models. It was especially informative in studies that established the important role of the renin-angiotensin system in proteinuria and kidney disease progression **(Eddy *et al.* 2012).** The effects of Lina versus telmisartan in preventing CKD progression in non-diabetic rats with 5/6 nephrectomy were compared. The results revealed that interstitial fibrosis was significantly decreased by 48% with Lina but non-significant with telmisartan. The urinary albumin-creatinine ratio was significantly decreased by 66% with Lina and 92% with telmisartan versus placebo. As shown by mass spectrometry, Lina up-regulated peptides derived from collagen type I, apolipoprotein C1, and heterogeneous nuclear ribonucleoproteins A2/B1, a potential downstream target of atrial natriuretic peptide, whereas telmisartan up-regulated angiotensin II. A second study was conducted to confirm these findings in 5/6 nephrectomy wild-type and genetically deficient DPP-4 rats treated with Lina or placebo where Lina therapy in wild-type rats was as effective as DPP-4 genetic deficiency in terms of albuminuria reduction **(Tsuprykov *et al.* 2016)**. **Hasan and colleagues (2019)** investigated the renal effects of Lina in GLP-1 receptor knockout (Glp1r-/-) and wild-type mice with 5/6 nephrectomy where Lina treatment significantly attenuated renal interstitial fibrosis in wild-type and Glp1r-/- mice as indicated by suppressed plasma cystatin C and creatinine levels and increased renal gelatinase/collagenase, matrix metalloproteinase-1 and -13 activities. The proteomics as well as Western blot and immunofluorescence study results showed that Lina treatment

significantly upregulated collagen α-1, thymosin β4, and heterogeneous nuclear ribonucleoprotein A1 and significantly downregulated Y box binding protein-1. Additionally, Lina significantly counteracted the upregulation of renal TGF-β1 and pSmad3 expression in wild-type and Glp1r-/- mice. The study concluded that Lina proved a renoprotection in non-diabetic CKD without involving GLP1/ GLP-1 receptor mediated pathways.

3.5. Randomized clinical trials

The renoprotective effects of Lina were evaluated in randomized clinical trials designed to explore both cardiovascular and kidney outcomes the randomized, controlled 'efficacy, safety and modification of albuminuria in type 2 DM subjects with renal disease with linagliptin' (MARLINA-T2D) study, which concluded that Lina was associated with significant improvements in glycemic control with a non-significant reduction in albuminuria **(Kanasaki 2018)**. The 'cardiovascular and renal microvascular outcome study with linagliptin in patients with type 2 DM' (CARMELINA), a randomized, placebo-controlled, multicenter non-inferiority trial conducted from 2013 to 2016 in 27 countries at 605 clinic sites among 6980 adults patients with type 2 DM which concluded that Lina was associated with a significant reduction in albuminuria **(Rosenstock *et al.* 2019)**.

4. Mechanisms of linagliptin renoprotection

4. 1. Antifibrotic effects

Shi *et al.* (2015) reported that Lina directly targets the interaction of DPP-4 with integrin β1, preventing endothelial-mesenchymal transition and ultimately renal fibrosis. Moreover, the study of **Takashima *et al.* (2016)** showed that DPP-4 inhibition by Lina, independent of GLP-1 receptor signaling, contributes to protection of the diabetic kidney through SDF-1-dependent anti-oxidative and anti-fibrotic effects and amelioration of adverse renal hemodynamics. In addition, **Gangadharan *et al.* (2015)** described that the cation-independent mannose-6-phosphate receptor facilitates the conversion of latent to active TGF-β1 in renal proximal tubular cells and Lina reduces this conversion with downstream reduction in fibronectin transcription. Furthermore, the influences of sDPP4 on renal epithelial cells were demonstrated by **Huang *et al.* (2023)** via measuring the expression of EMT markers and ECM proteins, where the study results showed that sDPP4 upregulates the EMT markers actin alpha 2 and collagen type I α-1 and increases total collagen content. Additionally, sDPP4 activates TGF-βR / Smad signaling in renal epithelial cells, whereas treatment with Lina, abrogates the effect of sDPP4 on EMT.

4.2. Antioxidant and free radical scavenging properties

The antioxidant properties of Lina have not been shared with other DPP-4 inhibitors. In contrast to other agents in this class, Lina contains a xanthine backbone and can inhibit xanthine oxidase, an enzyme involved in purine metabolism that generates ROS

(Daza-Arnedo *et al.* 2021). It has been reported that Lina attenuates ROS by activating the Nrf2/HO-1 signaling pathway in immortalized rat renal tubular epithelial cell lines (NRK-52E cells) on an AKI model of endotoxic shock induced by LPS **(Wu *et al.* 2021)**. A parallel effect was previously documented by the study of **Mima *et al.* (2020)** in which Lina offers protection against diabetic kidney injury partially *via* activating the Keap1/Nrf2 pathway on the high glucose-induced podocyte apoptosis model. Furthermore, **Spencer and colleagues (2018)** described that Lina ameliorates albuminuria and kidney hypertrophy in diabetic DBA/2J mice and increases the mRNA and protein levels for the antioxidants catalase and MnSOD in glucose-6-phosphate dehydrogenase deficient mice.

4.3. Anti-inflammatory effect

The study of **Tang *et al.* (2021)** demonstrated that the C-reactive protein (CRP) promotes diabetic renal injury with more severe renal inflammation and fibrosis in db/db mice. Also, their immunohistochemistry study detected an enhancement of pro-inflammatory cytokines and chemokines including TNF-α, IL-1β, and monocyte chemoattractant protein 1 (MCP-1) and renal fibrotic biomarkers (collagen I and IV) in the diabetic injured kidney of transgenic CRP^{tg} db/db mice compared with db/db mice, while inhibition of DPP-4 with Lina significantly reduced the CRP-driven inflammation and fibrosis in the transgenic animal group. Moreover, they observed that Lina treatment was capable of blocking the DPP4/CD32b/NF-κB circuit in CRP-mediated diabetic kidney, as shown by the significant CD32b suppression and NF-κB inactivation in the Lina-treated CRP^{tg} db/db mice. Additionally, **Wu *et al.* (2021)** also stated that the renoprotective effects of Lina were attributed to its anti-inflammatory effect by inhibiting the pro-inflammatory cytokines TNF-α and IL-1β, as well as, suppressing NF-κB and iNOS in the rat model of endotoxin-shock-induced AKI. Furthermore, a previous study in a rat model of doxorubicin nephropathy concluded that Lina had an anti-inflammatory effect, which was explained by the suppression of the NLR containing pyrin domain 3 (NLRP3) inflammasome IL-1β and IL-6 upregulations **(Jo *et al.* 2018)**.

4.4. Anti-apoptotic effect

The effect of Lina on apoptosis and related biomarkers was reported *in vivo* and *in vitro* studies. The study of **Tanaka *et al.* (2016)** showed that Lina attenuates free fatty acids-bound albumin-induced tubular inflammation and fibrosis in cultured mouse proximal tubular cells as indicated by inhibition of the TUNEL-positive cells and decreased cleavage of caspase-3 as well as downregulated mRNA expression of inflammatory mediator MCP-1. In addition, the study of **Korbut *et al.* (2020)** reported that Lina alone or in combination with empagliflozin significantly decreases the expression of apoptotic markers caspase-3 and Bcl-2 in db/db mice model of DKD.

5. Conclusion

The renoprotective effects of Lina were clinically proven and extensively studied in different experimental models of acute and CKD. The protective effects on the kidneys appear to be pleiotropic, with diverse mechanisms. These mechanisms include reducing oxidative stress, increasing endogenous antioxidant defense capacities, opposing inflammation by inhibiting NF-kB and inflammatory cytokines release, reducing renal fibrosis, and decreasing apoptotic cell death. The ultimate goal of Lina treatment, regardless of the kidney injury models and protective mechanisms discovered, is to improve kidney function. As a result, Lina shows potential as a treatment for kidney disorders. However, Further studies, are suggested in experimental models of non- DKD such as nephrotoxicity and unilateral ureteral obstruction models. In addition, the non-diabetic preclinical studies need confirmation in ongoing interventional clinical trials.

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الدور الوقائى لمثبط انزيم ثنائى الببتيديل ببتيداز-٤ , لیناجلیبتین فى حالات الاعتلال الكلوى الحادة والمزمنة

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الملخص العربى

مثبطات ثنائى الببتيديل ببتيداز-٤ هي فئة من مضادات السكرى المعتمدة للعلاج عن طريق الفم للمرضى الذين يعانون من داء السكري من النوع الثانى والتي تعمل من خلال منع انحلال هرمونات الإنكريتين التي تلعب دورًا مهمًا في إفراز الأنسولين وتنظيم نسبة الجلوكوز في الدم. كما تتمتع مثبطات ثنائى الببتيديل ببتيداز-٤ بالقدرة على تقديم تأثيرات مفيدة تتجاوز خفض الجلوكوز والتي تكمن في القدرة الوظيفية لإنزيم ثنائى الببتيديل ببتيداز-٤ على تقطيع مجموعة متنوعة من الببتيدات بصرف النظر عن الإنكريتينات التي أثبتت تأثيراتها على الكلى والقلب والأوعية الدموية. يختلف دواء لیناجلیبتین عن امثاله من نفس النوع بأنه المركب الوحيد الذي يتم التخلص منه بشكل رئيسي عبر مسار غير كلوي، لذا فإن انخفاض معدل الترشيح الكبيبي لا يتطلب تعديل الجرعة. بالإضافة إلى ذلك، يعتبر لیناجلیبتین الوحيد فى مجموعته الذي تم تحديده و تم تقييمه في تجربة سريرية عشوائية مصممة لإجراء تقييم شامل لنتائج أمراض القلب والكلى لدى المرضى الذين يعانون من مرض السكري من النوع الثانى. وتقدم هذه المراجعة لمحة موجزة عن التجارب الحالية التى تم اجرائها في النماذج التجريبية لامراض الكلى الحادة والمزمنة و كذلك الدراسات السريرية حول التأثيرات الوقائية لليناجليبتين مع القاء بعض الضوء على آليات الحماية الأساسية.

الكلمات المفتاحية: مثبطات انزيم ثنائى الببتيديل ببتيداز-٤ ,مرض الكلى المزمن ,لیناجلیبتین ,التليف الكلوي ,الاعتلال الكلوى الحاد