Kidney fibrosis: emerging diagnostic and therapeutic strategies*

Barbara Mara Klinkhammer[1], Peter Boor[1,2,3]

[1] Institute of Pathology, RWTH Aachen University Hospital, Aachen, Germany

[2] Electron Microscopy Facility, RWTH Aachen University Hospital, Aachen, Germany

[3] Division of Nephrology and Immunology, RWTH Aachen University Hospital, Aachen, Germany

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Address correspondence to:

Peter Boor, MD, PhD
Institute of Pathology
RWTH Aachen University Hospital
Pauwelsstrasse 30
52074 Aachen, Germany
Phone: +49 241 80 85227
Fax: +49 241 80 82446
E-mail: pboor@ukaachen.de

Barbara Mara Klinkhammer
Institute of Pathology
RWTH Aachen University Hospital
Pauwelsstrasse 30
52074 Aachen, Germany
Phone: +49 241 80 37205
Fax: +49 241 80 82446
Email: bklinkhammer@ukaachen.de

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Highlights

- Fibrosis can affect all kidney compartments depending on the underlying disease.
- Fibrosis is the common endpoint of all progressive chronic kidney diseases, but there is no specific anti-fibrotic treatment available.
- The invasive kidney biopsy is currently the only way to specifically assess kidney fibrosis, but research on new liquid biomarkers and non-invasive imaging is progressing.
- There are extremely few clinical trials testing specific anti-fibrotic agents for kidneys.
- Rapidly increasing kidney fibrosis research fueled by new omic technologies provides great potential for identifying new biomarkers and targets for treatments.

Abstract (114)

An increasing number of patients worldwide suffers from chronic kidney disease (CKD). CKD is accompanied by kidney fibrosis, which affects all compartments of the kidney, i.e., the glomeruli, tubulointerstitium, and vasculature. Fibrosis is the best predictor of progression of kidney diseases. Currently, there is no specific anti-fibrotic therapy for kidney patients and invasive renal biopsy remains the only option for specific detection and quantification of kidney fibrosis. Here we review emerging diagnostic approaches and potential therapeutic options for fibrosis. We discuss how translational research could help to establish fibrosis-specific endpoints for clinical trials, leading to improved patient stratification and potentially companion diagnostics, and facilitating and optimizing development of novel anti-fibrotic therapies for kidney patients.

1. Relevance of kidney fibrosis (1023)

Chronic kidney disease (CKD) affects between 7–12% of the world's population and became a global medical problem (Collaboration, 2020; Hallan et al., 2006; Romagnani et al., 2017). The prevalence is steadily increasing, given demographic trends with aging populations, and the persistently high prevalence of risk factors such as diabetes, hypertension, and obesity (Couser et al., 2011; Jha et al., 2013). In 2017, estimated 1.2 million people died from CKD and in 2019, CKD ranked 18th among all causes of death, and 8th among 50-74 years old people (Diseases and Injuries, 2020). CKD is projected to be the 5th main cause of death by 2040 (Foreman et al., 2018). Patients with kidney diseases are the most complex and multi-morbid patient populations in internal medicine (Tonelli et al., 2018).

Kidney fibrosis is a consequence of any kind of severe or ongoing injury and a common feature of CKD. Fibrosis is an active process, directly contributing to the development and progression of CKD, which can ultimately lead to end-stage kidney disease (ESKD). Kidney fibrosis has also been implicated in the development of various complications of CKD, such as hypertension, cardiovascular disease, and anemia. Therefore, targeting kidney fibrosis represents a promising strategy for the prevention and treatment of CKD and ESKD.

The development of kidney fibrosis is a dynamic process involving the complex interplay between numerous cell types, secreted factors, extracellular vesicles, and extracellular matrix (ECM) (Figure 1). Under normal conditions, kidney fibroblasts are quiescent and maintain the homeostasis of the ECM through a balance between ECM synthesis and degradation. During normal injury repair, activation of fibroblasts leads to transient fibrosis. This fibrosis is likely reversible, however, there is currently no definition of "normal" fibrosis, and relatively little is known about it (Boor and Floege, 2012; Schuster et al., 2023). In response to extensive or repetitive injury, an imbalance between the synthesis and degradation of ECM proteins occurs, leading to pathological fibrosis. Fibrosis affects all kidney compartments, the glomerulus, termed glomerulosclerosis, vasculature, termed arterio- and arteriolosclerosis, and tubulointerstitium, termed interstitial fibrosis (Bulow and Boor, 2019). The extent to which each compartment is affected depends on the underlying cause, i.e., glomerular diseases lead

primarily to glomerulosclerosis, vascular diseases to arteriosclerosis, and tubulointerstitial disease to interstitial fibrosis. Given the intrinsic connection between the kidney compartments, injury and fibrosis in one compartment can lead and spread to other compartments, e.g., from the glomeruli to the interstitium. In advanced CKD, it is not uncommon to observe advanced fibrosis in all compartments, which does not allow the identification of the primary site and cause of fibrosis.

Activated fibroblasts with low α-smooth muscle actin expression and myofibroblasts, i.e., specialized α-smooth muscle actin expressing cells with contractile properties, are key players in fibrosis. Their exact definition and origin are still controversial, but both were found to be heterogeneous populations arising from a variety of sources, with resident mesenchymal cells, particularly resident fibroblasts and pericytes, being the major source (Boor and Floege, 2012; Kramann et al., 2015; Kuppe et al., 2021; LeBleu et al., 2013; Schreibing et al., 2023; Schuster et al., 2023). These cells expand, produce, and deposit ECM proteins, such as collagens and fibronectin, and change the mechanic properties of the tissue leading to fibrosis and loss of normal kidney architecture and function (Figure 1).

Preclinical studies consistently showed the potential of therapeutic approaches targeting kidney fibrosis, including pharmacological, gene, or cell-based therapies (Boor et al., 2010; Djudjaj and Boor, 2019; Klinkhammer et al., 2017; Liu et al., 2021; Ruiz-Ortega et al., 2020). These approaches target fibroblast activation, inhibit ECM production, or promote ECM degradation. Despite the promising preclinical results, till now, none of the approaches has made it to clinical practice. The poor translation in the kidney field has several reasons and is reflected by nephrology having the lowest number of randomized clinical trials (RCTs) in all internal medicine disciplines (Floege et al., 2015; Klinkhammer et al., 2017; Palmer et al., 2011; Samuels and Molony, 2012). Clinical trials in nephrology are hampered by the typically slow progression of renal disease and the heterogeneity of patient populations. Some new short-term surrogate endpoints for trials were approved by the authorities, like the food and drug administration (FDA). This included remission of nephrotic syndrome, but this only applies to some rare glomerular diseases (Thompson et al., 2015). Other surrogate endpoints included

the reduction of proteinuria or albuminuria in glomerular diseases (Heerspink et al., 2019), but these relatively non-specific endpoints do not distinguish between disease activity, hemodynamic effects, or scar formation. Change in the slope of estimated glomerular filtration rate (eGFR) (Inker et al., 2019) is another surrogate endpoint, which is not sensitive, prone to pre-analytic errors (e.g., diet changes, weight changes), and compensatory hyperfiltration in remaining nephrons can blunt eGFR changes. Such adaptive hyperfiltration of remnant nephrons masks the initial presence of fibrosis and can lead to perpetuated structural damage and further CKD progression (Hostetter et al., 1981; Klinkhammer et al., 2022; Romagnani et al., 2017). Despite the advantages of the newer endpoints over the classical “DDD-endpoints” (death, dialysis, doubling of serum creatinine), they remain unspecific for underlying diseases and fibrosis.

For more than 20 years the conventional preservative treatment for CKD patients comprises recommendations for diet and life-style changes, e.g., low salt intake, weight loss, moderate physical activity, and pharmacological blood pressure medication in form of the renin–angiotensin system (RAS) blockade using angiotensin-converting enzyme (ACE) inhibitors and/or angiotensin receptor blockers (ARBs) or mineralocorticoid receptor blockers. Clinical trials are still being conducted to expand the group of patients who could further benefit from these treatments, e.g., the effects of Ramipril in the “Early Prospective Therapy Trial to Delay Renal Failure in Children With Alport Syndrome” (phase 3, https://clinicaltrials.gov/ct2/show/NCT01485978) or Atrasentan in “A Phase 3, Randomized, Double-blind, Placebo-controlled Study of Atrasentan in Patients With IgA Nephropathy at Risk of Progressive Loss of Renal Function” (https://clinicaltrials.gov/ct2/show/NCT04573478) (Gross et al., 2020). Depending on the primary disease additional specific drugs are given, e.g., immunosuppressors for immune-mediated disorders or glucose-lowering agents for patients with diabetes mellitus (DM). Further drugs for the management of anemia or bone disorders are used to slow or prevent CKD complications (Kalantar-Zadeh et al., 2021).

There is no treatment directly targeting kidney fibrosis. Instead, the current strategy is the prevention of the transition of kidney diseases, particularly acute kidney disease to CKD or the

progression of CKD with the above-mentioned interventions (Ruiz-Ortega et al., 2020). Only very few clinical trials testing anti-fibrotic interventions were conducted in nephrology and were summarized by us and others (Klinkhammer et al., 2017; Liu and Zhuang, 2019). Here, we provide an update on the ongoing interventional clinical trials since the last review in 2017. We also provide an overview of emerging fibrosis diagnostics with a particular emphasis on liquid biomarkers and non-invasive imaging in clinical trials and discuss their potential in combination with recent advances in preclinical research to advance the clinical management of fibrosis in CKD.

2. Emerging diagnostics: liquid biomarkers (1228)

Early detection and accurate assessment of kidney fibrosis are crucial for timely interventions. Kidney biopsies remain the gold standard for assessing kidney fibrosis, but they are invasive, have potential complications, and are not suitable for monitoring (Whittier and Korbet, 2004). The estimation of fibrosis in biopsies is largely performed subjectively by pathologists (Najafian et al., 2022). Therefore, non-invasive and quantitative biomarkers specifically reflecting kidney fibrosis would be of great value and represent an active area of research.

The KDIGO (Kidney Disease Improving Global Outcomes) guidelines recommend using the eGFR, proteinuria and urine sediment abnormalities as laboratory biomarkers for assessing the risk of CKD and its progression (KDIGO, 2013). However, none of these specifically reflect fibrosis, particularly in the early stages. Several alternative fibrosis-specific biomarkers in blood or urine have been proposed, including cytokines, chemokines, growth factors, miRNAs (microRNAs, small non-coding RNAs) or the composition of extracellular vesicles (Barinotti et al., 2022; Zhang et al., 2016). Transforming growth factor-beta 1 (TGF-β1) is a key cytokine in the pathogenesis of kidney fibrosis (Meng et al., 2016). TGF-β1 was shown in several studies to be elevated in urine and plasma from patients with CKD and correlate with the degree of

fibrosis, similarly to miRNAs related to TGF-β-signaling (Muralidharan et al., 2017; Naicker et al., 2021; Ren et al., 2019; Trnka et al., 2012). miRNAs have several advantages as biomarkers, including tissue specificity, stability in body fluids, where they are normally found in protein complexes or extracellular vesicles, and the ability to detect early-stage disease (Li et al., 2021a). Several miRNAs have been proposed as biomarkers of kidney fibrosis, including miR-21, miR-29, and miR-Let7b (Mahtal et al., 2022; Peters et al., 2020). Compared to blood miRNAs or single miRNAs, urinary miRNAs panels, analyzed from urinary extracellular vesicles/exosomes, were more effective diagnostic biomarkers for CKD with higher sensitivity and specificity (Chun-Yan et al., 2018; Li et al., 2021a; Miranda et al., 2010). An observational clinical trial investigates the utility of urinary exosomes for fibrosis diagnostics and prediction of outcomes in transplant kidneys (Table 1). The approach is to extract the urinary exosomes and perform proteomics analysis and RNA-sequencing at the time of transplantation.

A prospective trial in kidney transplant patients investigated urinary markers of fibrosis with a particular focus on connective tissue growth factor (CTGF) (Table 1), but the results are not available. Previously, a retrospective single-center study in kidney transplant patients found that urinary and kidney tissue CTGF three months after transplantation were independent predictors of interstitial fibrosis and tubular atrophy (IF/TA) at 5 years after transplantation (Vanhove et al., 2017).

Serum and plasma markers, such as soluble urokinase-type plasminogen activator receptor (suPAR), galectin-3, fibroblast growth factor 23 (FGF-23) and α-Klotho, have been associated with kidney fibrosis in various CKD patient populations (Chang et al., 2020; Genovese et al., 2014; Manou et al., 2020; O'Seaghdha et al., 2013; Rebholz et al., 2018; Weidemann et al., 2020). Monocyte chemoattractant protein-1 (MCP-1) has been implicated in kidney fibrosis and its levels in urine and plasma were elevated in patients with CKD and correlated with the degree of fibrosis (Amatruda et al., 2022; Schrauben et al., 2021). MCP-1 is likely a marker of inflammation, which is commonly observed in fibrotic tissue. Similarly, other suggested urinary biomarkers of fibrosis like Tumor necrosis factor-alpha receptor type 1 and type 2 (TNFR1+2), suPAR or Chitinase-3-like protein 1 (CHI3L1 or YKL-40) might not be fibrosis specific (Sandokji

and Greenberg, 2021). Also, markers of tubular injury likely do not reflect fibrosis specifically, e.g., urinary neutrophil gelatinase-associated lipocalin (NGAL) or kidney injury molecule-1 (KIM-1), that have been tested in CKD patients (Barinotti et al., 2022; Meena et al., 2023). One clinical trial used furosemide stress test in CKD patients (https://clinicaltrials.gov/ct2/show/study/NCT02417883Table 1) (Koyner et al., 2015; Rivero et al., 2020), showing an inverse correlation between the degrees of fibrosis in biopsy and urine volumes and furosemide excretion. Although this test was suggested as a potential non-invasive tool to evaluate interstitial fibrosis (Rivero et al., 2020), it is only based on association and is unlikely fibrosis specific.

More specific and direct biomarkers of fibrosis could be components of the ECM. The urinary and circulating procollagen type III N-terminal propeptide (PIIINP) was shown to have a strong positive correlation with the severity of kidney fibrosis in chronic nephropathy patients (Soylemezoglu et al., 1997). This was confirmed for urinary PIIINP in CKD patients (Ghoul et al., 2010), and in transplant kidneys also predicting outcome (Teppo et al., 2003; Yilmaz et al., 2017). Urinary PIIINP was associated with CKD progression and death (Ix et al., 2015; Park et al., 2017). Other proposed markers were Pro-C3, an N-terminal propeptide of type III collagen better representing the collagen III deposition, and C3M, a collagen III degradation fragment (Nielsen et al., 2013). Urinary Pro-C3 and C3M, and their ratio, reflected fibrosis and CKD stage, CKD progression and risk indicators for death in animals and CKD patients (Genovese et al., 2016; Genovese et al., 2021b; Hijmans et al., 2017). Similarly, collagen VI production and degradation fragments also showed promising results. A part of the C5 domain of collagen VI alpha 3, which is cleaved during collagen VI production, was termed endotrophin. This fragment is also known as Pro-C6, and acts as a matrikine, a peptide fragment from an ECM protein with different biological activity then the original protein. Endotrophin was first described to have pro-fibrotic, pro-angiogenic and pro-inflammatory effects in malignant tumor progression but also plays a role in metabolic regulations and insulin resistance as well as in fibrotic diseases *via* TGF-β1 regulation (Park and Scherer, 2012; Williams et al., 2022). Pro-C6/endotrophin level in serum and urine correlated with kidney

function, CKD stage and interstitial fibrosis in patients with Lupus Nephritis, IgA Nephropathy and ANCA-associated vasculitis (Genovese et al., 2021a; Neprasova et al., 2023; Sparding et al., 2022). Endotrophin predicted CKD progression, associated with graft failure in transplant recipients was independently associated with mortality (Fenton et al., 2017; Kremer et al., 2022; Rasmussen et al., 2017). It remains unclear, which of these ECM markers might be suitable to monitor fibrosis and if they complement each other. Given that fibrotic processes are similar in all organs and tissues, none of these markers is specific for kidney fibrosis, even if analyzed in the urine. Also, their amounts will likely depend on the extent of fibrosis and affected tissue, e.g., even slight fibrosis in the liver, weighing 1.5 kg, might likely result in more circulating ECM than more advanced fibrosis in kidneys, both weighing around 0.3-0.4 kg.

Challenges in the interpretation of biomarkers studies were shown in a meta-analysis of plasma and urine biomarkers for CKD outcomes from 129 studies selected from 26,456 abstracts. This already suggests the relatively small number of studies qualifying for meta-analysis. The meta-analysis found that plasma TNFR1 and 2, FGF23, Kidney injury molecule-1 (KIM-1), and suPAR were the most frequently investigated markers, but the conclusion about their performance was limited due to the heterogeneity of study cohorts, designs and analytical approaches (Liu et al., 2022a). One example is the measurement of suPAR in children with CKD (“Chronic Kidney Disease in Children (CKiD) Study”, NCT00327860). One publication from this cohort found plasma suPAR not being independently associated with CKD progression (Greenberg et al., 2020), while another study of the same cohort found a positive correlation (Weidemann et al., 2020). A third study identified the reasons for this discrepancy, being different sample selection (not 100% inclusion of the same study subjects), different suPAR assays with different sample preparation and dilution, different covariates, and different statistical analyses. These findings highlight the importance of repeatability and validation, transparency in data presentation and choice of comparable metrics (Abraham et al., 2021).

Despite the first promising results of some liquid biomarkers for kidney fibrosis, several challenges remain, e.g., standardization of sample collection and assays, heterogeneity of CKD and analyzed cohorts or costs and availability of biomarker assays. The development of

multiplex assays enabling the measurement of multiple biomarkers simultaneously in one sample may enhance diagnostic accuracy and predictive value. E.g., panels for collagen peptides enabled the identification of different collagen remodeling profiles even in patients with similar renal function. This might provide new insights into different disease phenotypes with different disease activities which were not distinguishable based on classical renal function parameters (Magalhaes et al., 2017; Rasmussen et al., 2019). As for other novel technologies, the clinical value remains to be analyzed in well-controlled and designed studies.

Table 1: Selected clinical studies testing new diagnostics for kidney fibrosis.

The search was performed on https://clinicaltrials.gov/ including trials between 2016 and march 2023. Each method is sorted by starting date.
ACR = albumin-creatinine ratio, BP = blood pressure, CKD-EPI = chronic kidney disease epidemiology collaboration, DSA = donor-specific antibody, eGFR = estimated glomerular filtration rate, IF/TA = interstitial fibrosis/tubular atrophy, IVIM-DWI = intravoxel incoherent motion diffusion-weighted imaging, LDH = lactate dehydrogenase, MRE = magnetic resonance elastography, MRI = Magnetic Resonance Imaging, NGAL = neutrophil gelatinase-associated lipocalin, PIIINP = procollagen III aminoterminal peptide N, RRT = renal replacement therapy, uCTGF = urinary connective tissue growth factor, US = ultrasound

Method	Official Title	Status	Phase, Sponsor	Key Inclusion Criteria	Primary Outcome Measures	Results	URL
Liquid biomarker							
urinary connective tissue growth factor (uCTGF)	Prospective Study of Urinary Connective Tissue Growth Factor and Related Pro-fibrotic Mediators as Potential Early Biomarkers of Progressive Renal Allograft Fibrosis in de Novo Kidney Recipients	Unknown, started July 2015	Universitair e Ziekenhuize n KU Leuven	- Patients who receive a primary or secondary single cadaveric or living donor renal allograft - Signed informed consent	- Allograft interstitial fibrosis (scored according to revised Banff 1997 criteria) in consecutive protocol biopsies [Time Frame: 24 months post-transplantation]	n.a.	https://clinicaltrials.gov/ct2/show/NCT01982903
Urine excretion after Furosemide test	Furosemide Stress Test as a Predictor of Tubular Atrophy and Interstitial Fibrosis in Patients With Chronic Kidney Disease (FST-IFTA)	Unknown, started April 2015	Instituto Nacional de Cardiologia Ignacio Chavez	- Accept to participate (informed consent) - Legal age or older - An estimated glomerular filtration rate greater than 15ml/min/1.73m^2, calculated by CKD-EPI	- Urinary Output [Time Frame: 6 hours] - *among the secondary outcome parameters:* *Interstitial Fibrosis in kidney biopsy* *[Time Frame: 3 days]* *Measure interstitial fibrosis in kidney biopsy*	(Rivero et al., 2020)	https://clinicaltrials.gov/ct2/show/results/NCT02417883
Urinary Transglutaminase 2	Development of a Diagnostic Kit for Urinary Transglutaminase 2 as a Biomarker for Kidney Allograft Fibrosis	Unknown, started August 2017	Asan Medical Center	- Kidney transplant recipients from cadaveric or living donors - Kidney transplant recipients who take immunosuppressants regularly - Kidney transplant recipients who voluntarily agree to participate in this trial	- Change of level of urinary transglutaminase 2 [Time Frame: 3 days, 7 days, 1 month, 3 months, 6 months post-transplant]	n.a.	https://clinicaltrials.gov/ct2/show/NCT03487861
Urinary exosomes	Multicenter, Prospective Observational Study to Identify and Validate a Composite of Urinary	Unknown, started March 2019	Asan Medical Center	- End-stage renal disease patients receiving kidney transplantation from deceased donors who have the ability to provide content for this study	- Kidney graft fibrosis on zero day biopsy [Time Frame: zero-day (time of transplant)]	n.a.	https://clinicaltrials.gov/ct2/show/NCT03870542

	Exosomal Biomarkers for Kidney Allograft Tubulointerstitial Fibrosis (UFO)						
MRI							
MRI (non-contrast multiparametric MRI (mpMRI) including T1 mapping, T1ρ and IVIM-DWI)	Characterization of Renal Allograft Fibrosis and Prediction of Outcome Using a Quantitative MRI Approach	Enrolling, since February 2022	Weill Cornell Medicine, Icahn School of Medicine at Mount Sinai	- Acute or chronic allograft dysfunction, referred for biopsy based on clinical grounds (indication biopsy) - Stable allograft function and donor-specific antibody (DSA) positivity, referred for surveillance biopsy at 3 and 12 months post transplantation - Informed consent for this study. - Recruitment of patients after 1 month post-transplant period since the early post transplant course is associated with increased risk of acute dysfunction - Healthy volunteers with no renal disease will be recruited for protocol optimization and to serve as controls. - Potential renal donors undergoing clinical non-contrast or contrast-enhanced MRI will be recruited to serve as controls	- Presence of renal allograft fibrosis in biopsies - Banff scoring system for fibrosis [Time Frame: 2 weeks after renal allograft biopsy]	-	https://clinicaltrials.gov/ct2/show/NCT05058170
MRI	Noninvasive Evaluation of Renal Allograft Fibrosis by MRI	Enrolling by invitation, since August 2021	Mayo Clinic	- Age 18-80 years - Recipient of living donor kidney transplantation 4 or 7 years earlier - Competent and able to provide written informed consent; - Ability to comply with protocol	- The values and correlation of qMT(f) with tissue fibrosis (trichrome) [Time Frame: 2 years]	-	https://clinicaltrials.gov/ct2/show/NCT04899167
MRI (multiparametric, T1 relaxation time mapping; DWI; Phase Contrast MRI; ASL; BOLD mapping)	Application of Functional Renal MRI to Improve Assessment of Chronic Kidney Disease (AFiRM)	Recruiting, since June 2021	University Hospitals of Derby and Burton NHS Foundation Trust	- Age 18-75 years - CKD category G3-4 or CKD category G1-2 with overt albuminuria (urine ACR>30mg/mmol) - Informed consent	- CKD progression (doubling of serum creatinine, eGFR<15ml/min or RRT) OR a 40% decline in eGFR) [Time Frame: 10 years] - *among the secondary outcome parameters:* *Renal histology measures (Glomerulosclerosis score, extent of interstitial fibrosis, inflammation, peritubular capillary density, collagen accumulation, inflammatory cell subtypes)*	-	https://clinicaltrials.gov/ct2/show/NCT04238299
MRI (multiparametric: diffusion weighted MRI, T1-mapping and T2-mapping, T1-rho and arterial-spin labelling)	Detection of Renal Fibrosis and Prediction of Kidney Function Decline: The Role of MRI and Markers of Accelerated Renal Ageing (MARS)	Recruiting, since January 2021	University Hospital, Akershus	- >18 years of age, Scheduled for a kidney biopsy for diagnostic purposes at the Department of Nephrology, Akershus University Hospital will be invited to participate in the study	- Correlation of between degree of renal fibrosis determined by a multiparametric MRI protocol and gold-standard morphometric evaluation of renal fibrosis in renal biopsies at baseline (time of scheduled renal biopsy) and after two years [Time Frame: 5 years]	-	https://clinicaltrials.gov/ct2/show/NCT04625140
MRI (Magnetic Resonance Elastography (MRE))	Magnetic Resonance Elastography of Transplanted Kidney (GREFFE_ELASTO IRM)	Completed, July 2019-December 2020	University Hospital, Bordeaux	- Age ≥ 18yrs - Transplanted kidney patient with suspicion of IF/TA lesions requiring biopsy graft sampling under ultrasound control - Signed informed consent - Health insurance	- Mean value of renal elasticity [Time Frame: Baseline (defined as during MRE exam)] - *among the secondary outcome parameters:* *pathological damage (semi-quantitatively by the pathologist following the Banff classification)*	(Chauveau et al., 2022)	https://clinicaltrials.gov/ct2/show/NCT03918161
MRI (Multi-parametric renal MRI)	Pathology and Imaging in Kidney Allografts (PIKA)	Terminated February 2019-May 2022 (recruitment difficulties due to impact of COVID-19 pandemic) Start February 2019	NHS Greater Glasgow and Clyde, University of Glasgow	- Age > 18 years - Recipient of a kidney transplant - Referred for clinically indicated biopsy of transplant kidney - Ability to comply with study procedures. - Ability to give informed consent.	- Comparison of MRI biomarkers for fibrosis with histology [Time Frame: Baseline]	29 participants enrolled, (Rankin, 2022)	https://clinicaltrials.gov/ct2/show/NCT03780101
MRI	Development of Novel MRI Methods for Detecting and Measuring Renal Injury/Fibrosis	Completed, August 2018- June 2021	Children's Hospital Medical Center, Cincinnati	- ≥ 10 and ≤ 25 years of age - Kidney transplant patients, who have had a recent kidney biopsy (within 1 year) that shows interstitial fibrosis OR	- Development of noninvasive MRI methods (MR elastography, quantitative T1 mapping, T1rho mapping, T2 mapping, magnetization transfer imaging, diffusion-weighted imaging) to measure kidney disease	n.a. (37 participants enrolled)	https://clinicaltrials.gov/ct2/show/NCT03964948

				- Patients with CKD Stage 2-5 who have previously had a biopsy (within 1 year) OR - Lupus patients with active nephritis who will undergo biopsy evaluation before and after induction therapy OR - Healthy Controls	[Time frame: 3 years]		
MRI (multiparametric, T1 relaxation time and diffusion)	Using MRI ASL Techniques for Quantitative Measurement of Renal Haemodynamics and Structural Parameters in Acute Kidney Injury and Chronic Kidney Disease (REMIND)	Unknown, October 2015-December 2020	University of Nottingham	AKI Patients: - Acute Kidney Injury stage 2/3 (duration >24 hours) including patients requiring renal replacement therapy - >18 years & < 95 years - Informed consent CKD Patients: - Patients with CKD Stage 3-4 (eGFR> 20 and <60 ml/min) - >18 years & < 95 years - Informed consent	- The difference between volume (mls) MR parameter between healthy volunteers and patients with CKD and AKI [Time Frame: 3 years] - The difference between T1 (ms) MR parameter between healthy volunteers and patients with CKD and AKI [Time Frame: 3 years] - The difference between Diffusion weighted imaging MR parameter between healthy volunteers and patients with CKD and AKI - [Time Frame: 3 years] - *among the secondary outcome parameters:* *Correlations between structural T1 (ms) or DWI and blinded renal biopsy measurements (Sirius red fibrosis scoring)*	(Buchanan et al., 2021; Buchanan et al., 2020)	https://clinicaltrials.gov/ct2/show/NCT03578523
Ultrasound							
Strain Sono-Elastography (SE)	Validity of Strain Elastography for the Evaluation of Chronic Allograft Nephropathy	Completed, January 2021-october 2022	Kasr El Aini Hospital	- Renal transplant patients of more than 2 years duration, - Chronic allograft nephropathy proved by renal biopsy done within 1 month from the date of the strain elastography, - Body mass index less than 30 kg/m2, - Skin allograft distance of less than 3.5 cm, - Parenchyma thickness of more than 1 cm and no fluid accumulation around the allograft.	- Grade of fibrosis obtained by elastography [Time Frame: At the time of recruitment]	-	https://clinicaltrials.gov/ct2/show/NCT05682313
Shear Wave Elastography (SWE)	Evaluation of Kidney Graft's Fibrosis With Real Time Shear-wave Elastography (Elastogreffe)	Recruiting, since March 2019	University Hospital, Tours	- Kidney-transplanted patient, whatever kind of organ donation (alive donor, deceased donor included extended criteria Maastricht 2 or 3) > 18 years old	- Measure of shear wave elastography (as biomarker of kidney graft's fibrosis) [Time Frame: 3 months]	-	https://clinicaltrials.gov/ct2/show/NCT03819400
Ultrasound elastography (including SWE, B-mode, color, Doppler)	Application of Ultrasound Integrated Precision Diagnosis Technology in Prevention of Kidney Disease and Its Progress	Completed, April 2019 - June 2021	RenJi Hospital	- 18-70 years old - Cooperate with breath-holding, breath-holding and breath-exhaling movements - Communicate without obstacles. - Informed consent - Acute on Chronic Kidney Disease patients: abnormal renal pathology or glomerular filtration rate(GFR) (15 <GFR<90 ml/min.1.73 m2) or proteinuria > 1 g/24 h due to any cause. - Patients with kidney transplantation: Kidney transplant recipients in our hospital from May 2019 to November 2019	- Number of patients with creatinine increasing by more than 50% - Number of patients with initiation of continuous renal replacement therapy - Rate of death [Time Frame: 1-12 months]	(Zhu et al., 2022a; Zhu et al., 2022b)	https://clinicaltrials.gov/ct2/show/NCT04044404
Shear Wave Elastography (SWE))	Shear Wave Elastography in Native Kidney Disease: a Pilot Study	Terminated (Not enough participants recruited) July 2016-June 2018	Albert Einstein Healthcare Network	- Patients > 18 years of age who are referred for a native kidney biopsy	- Shear Wave Velocity of kidney parenchyma will be correlated with degree of fibrosis determined by a pathologist [Time Frame: 6 months]	n.a. (8 patients enrolled)	https://clinicaltrials.gov/ct2/show/NCT02830438
PET/CT							
[18F]AlF-NOTA-FAPI-04 PET/CT	Clinical Study of Fibroblast Activating Protein Inhibitor (FAPI) - Mediated 18F Targeted to Evaluate Inflammation and Fibrosis in Renal Diseases	Not yet recruiting, March 2023	Sichuan Provincial People's Hospital	- Nephritis or kidney fibrosis	- Standardized uptake value [Time Frame: 30minutes after PET/CT examination]	-	https://www.clinicaltrials.gov/ct2/show/NCT05752097

3. Emerging diagnostics: non-invasive imaging (1604)

Another emerging diagnostic approach for fibrosis is non-invasive imaging. Several imaging methods are available in clinics, including magnetic resonance imaging (MRI), sonography, nuclear imaging, mostly positron emission tomography (PET) and single-photon emission computed tomography (SPECT), and computed tomography (CT). Given the risk of contrast-induced nephropathy and exposure to ionizing radiation, CT does not seem to be a suitable approach for kidney fibrosis detection, and we have not found any studies focusing on CT in kidneys, while it is used for pulmonary fibrosis (Chen et al., 2020; Christe et al., 2019; Gotway et al., 2007). The utility of novel technologies, such as the single photon counting CT, which recently generated high-quality images at significantly lower radiation levels in kidney patients with urolithiasis, remains open (Niehoff et al., 2022).

The potential of MRI of kidneys is being increasingly recognized (Jiang et al., 2023; Rankin et al., 2022). MRI offers several advantages over other imaging modalities, including a lack of ionizing radiation, high spatial resolution, and the ability to provide both structural and functional parameters. Non-contrast MRI is currently preferred over contrast-enhanced MRI with Gadolinium-containing agents, given the previously reported risk of development of nephrogenic systemic fibrosis in patients with reduced kidney function (https://clinicaltrials.gov/ct2/show/NCT04776187, https://clinicaltrials.gov/ct2/show/NCT01467271) (Leyba and Wagner, 2019). Importantly, this risk seems to be restricted to only some linear formulations of the contrast agents, while others were shown to be safe even in dialysis patients (Abu-Alfa, 2020; Woolen et al., 2020).

Multiparametric MRI protocols allow the analysis of different features within one session. Those features include diffusion-weighted imaging (DWI, reflects tissue microstructure, e.g., decreases with fibrosis, inflammation) using apparent diffusion coefficient (ADC), T1 mapping (increases with fibrosis, inflammation, edema), blood oxygen level-dependent imaging (BOLD using T2, reflects tissue oxygen consumption) and arterial spin labeling (ASL, reflects renal

perfusion). A multi-center clinical trial used multiparameter MRI to assess kidney fibrosis in CKD (and AKI) patients who underwent kidney biopsy (Table 1). CKD study participants with “high” vs. “low” grade fibrosis in biopsy showed significantly higher values in cortical T1 and corticomedullary ADC and significantly lower corticomedullary ∆T1, cortical ADC, and ASL (Buchanan et al., 2020). The same trial also included AKI stage 3 patients who, at the time of AKI, exhibited an increased corticomedullary ∆T1 and reduced ASL, which persisted despite the recovery of kidney function at 1-year post-AKI, probably reflecting chronic subclinical damage. This could suggest that those patients are more prone to develop a further AKI episode or progress to CKD (Buchanan et al., 2021). DWI values in 122 CKD patients from the “CKD Optimal Management with Binders and Nicotinamide trial” (COMBINE, NCT02258074) were associated with a change in eGFR over time (Srivastava et al., 2020). This study did not include biopsies to correlate MRI with kidney fibrosis but showed that kidney functional MRI might be useful to identify patients at high risk of CKD progression. Another study with 80 CKD patients (60% with IgAN), showed that cortical DWI, T1, ASL values were significantly changed compared to healthy volunteers and correlated with interstitial fibrosis (Mao et al., 2022). A recent study with 46 IgAN patients confirmed that most MRI parameters significantly correlated with interstitial fibrosis (Liang et al., 2022). In contrast, in 20 transplant patients, cortical T1 inversely correlated with eGFR but there was no correlation between any MRI parameters and the percentage of cortical interstitial fibrosis analyzed in biopsies (Rankin, 2022). Comparisons and correlations of multiparametric MRI with renal histology from CKD patients were also planned in ongoing or recently completed trials (Table 1). The increased use of biopsy-controlled imaging studies is an important step. However, an important conceptual challenge with these studies is their associative character and the selection of the comparison cohorts and readouts from the biopsy. None of these studies provides sufficient evidence for any of the measured parameters to be fibrosis specific (Baues et al., 2017; Boor et al., 2015).

Magnetic resonance elastography is a technique using external mechanical vibration to generate shear waves and quantify tissue stiffness. Magnetic resonance elastography was tested as a surrogate marker of fibrosis in renal transplant patients

(https://clinicaltrials.gov/ct2/show/NCT03918161). It negatively correlated with glomerulosclerosis but not with interstitial fibrosis. Given that glomeruli provide only a very small proportion of kidney tissue, it seems unlikely that glomerulosclerosis could contribute to tissue stiffness detected by magnetic resonance elastography. Also, there was high interpatient variability between the mean stiffness values, even in the absence of allograft fibrosis, suggesting that this method might not be suitable for a specific measurement of kidney fibrosis (Chauveau et al., 2022). Taken together, MRI can provide detailed information on renal morphology, perfusion, and function, but data proving the specificity for fibrosis detection and quantification are still lacking. Also, the costs, access, and time-consuming procedure might limit the broad implementation of MRI as routine fibrosis diagnostics.

Ultrasound is a widely used non-invasive imaging modality for the evaluation of CKD. Its safety, low costs, and broad availability make it an attractive option for initial screening and follow-up of patients. Different ultrasound techniques, including B-mode imaging, Doppler imaging and contrast-enhanced ultrasound (CEUS), can provide accurate measurements of kidney size, parenchymal thickness, and renal blood flow (Singla et al., 2022). Ultrasound elastography is a technique that, like MRE, is used for the assessment of tissue stiffness. Two categories of ultrasound elastography have been tested in kidneys, i.e., strain elastography, measuring tissue displacement caused by external pressure, and shear wave elastography, measuring ultrasound-generated shear wave velocity.

A few studies reported a correlation between strain elastography and kidney fibrosis in transplant patients and one current clinical trial aims to validate these results (Table 1) (Gao et al., 2013; Orlacchio et al., 2014). However, due to the need for external compression and low tissue penetration, strain elastography is only useful for measures in renal allografts which are located closer to the body surface (Grenier et al., 2013; Jiang et al., 2023).

Shear wave elastography can be applied in transplant and native kidneys and its potential to measure kidney fibrosis and predict disease progression was primarily confirmed in several trials including patients with diabetic nephropathy (Hassan et al., 2016), glomerulonephritis (Grossmann et al., 2019) kidney transplantation (Qin et al., 2021) or mixed CKD populations

(Chen et al., 2022a, b; Leong et al., 2021; Samir et al., 2015; Zhu et al., 2022a). Those trials usually compared the shear wave elastography measures with fibrosis analyzed in kidney biopsies, as it will be also performed in two running trials (Table 1). In addition to the detection and quantification of fibrosis, some studies were also able to predict disease progression with shear wave elastography images (Sasaki et al., 2018; Zhu et al., 2022b).

A recent meta-analysis including six studies with 405 patients suggested that SWE has high accuracy in the diagnosis of kidney fibrosis. But various causes of renal fibrosis may result in differences in renal stiffness and therefore critical diagnostic thresholds cannot be generalized but probably need to be adjusted for specific cases (Mo et al., 2022). This might also be the reason why some studies reported no or only poor correlations between SWE and kidney fibrosis (Lee et al., 2015; Wu et al., 2023). It should be noted, that several factors can influence the quality and outcome of ultrasound results. Image acquisition (and interpretation) are operator dependent, and the physical shape of the patient may limit adequate diagnostic information. Studies to improve standardized methods could help to achieve more comparable results, e.g., for the assessment of kidney fibrosis in 190 CKD patients, the optimal measurement method of 2D-SWE was shown to be at a prone position in the renal middle part, and a measurement depth < 4 cm (Lin et al., 2023).

Taken together, ultrasound elastography might have a potential for fibrosis assessment, particularly given that it is very broadly available and cheap. However, the inconsistent data call for further, larger studies and efforts in standardized image acquisition. The potential of computational approaches like radiomics remains to be seen.

Another promising diagnostic approach for kidney fibrosis is non-invasive molecular imaging. Compared to other above-mentioned approaches, molecular imaging combines the possibility to specifically assess fibrosis-specific molecules within the kidneys. Molecular imaging uses molecular probes specifically targeting biological processes or molecules, that are coupled to contrast agents enabling *in vivo* visualization and quantification, e.g., using PET/SPECT or MRI or ultrasound (Baues et al., 2017; Klinkhammer et al., 2021; Mankoff, 2007). Nuclear imaging, i.e., PET and SPECT, has the advantage of being highly sensitive,

therefore requiring only very low amounts of molecular probes with radiotracers, and also allowing functional imaging.

In a pilot study testing a probe for fibroblast activation protein (FAP) in CKD patients, signals from PET-CT imaging after injection of the molecular imaging gadolinium-labeled probe [^{68}Ga]Ga-FAPI could differentiate mild, moderate and severe fibrosis analyzed in kidney biopsies (Zhou et al., 2021). The potential specificity of this approach was demonstrated by another study, in which renal parenchymal [^{68}Ga]Ga-FAPI uptake inversely correlated with GFR, which was not the case for other non-fibrosis directed probes [^{68}Ga]Ga-DOTATOC and [^{68}Ga]Ga-PSMA (Conen et al., 2022). Should FAPI imaging be validated in larger dedicated studies, as planned for 2023, and prove fibrosis-specific, it could represent the first directly applicable approach for specific non-invasive imaging of kidney fibrosis (Table 1) (Klinkhammer et al., 2021). The potential of FAPI-based PET imaging in non-cancer fibrotic diseases is currently also being explored in other organs, e.g., liver https://www.clinicaltrials.gov/ct2/show/NCT04533828, https://www.clinicaltrials.gov/ct2/show/NCT05262647 , https://www.clinicaltrials.gov/ct2/show/NCT04605939, lung https://www.clinicaltrials.gov/ct2/show/NCT05121779 , https://www.clinicaltrials.gov/ct2/show/NCT05365802, and heart https://www.clinicaltrials.gov/ct2/show/NCT04982458 , https://www.clinicaltrials.gov/ct2/show/NCT05356923 (Gu et al., 2022; Pirasteh et al., 2022; Rosenkrans et al., 2022; Sun et al., 2023; Wang et al., 2023; Yang et al., 2023).

Preclinical studies already showed the feasibility of molecular imaging of ECM components. Elastin-targeted MRI enabled non-invasive, longitudinal, and quantitative assessment of kidney fibrosis and monitoring of anti-fibrotic therapy effects in mice (Sun et al., 2019). The upregulation of the ECM target elastin in a variety of CKD and the specific binding of ESMA to human fibrotic kidneys *ex vivo* demonstrated the high translational potential of this approach (Sun et al., 2019). In a model of reversible kidney injury, elastin imaging detected ongoing fibrosis which was not identifiable *via* assessment of routine kidney function parameters

(Klinkhammer et al., 2022; Sun et al., 2019). Another study showed *in vivo* optical imaging of kidney fibrosis using a peptide termed CNA35, which binds with high affinity to collagen type I and III (Baues et al., 2019; Sanders et al., 2011). Similar to FAPI, both, CNA35 and ESMA, had already been employed to visualize collagen deposition in other organs, e.g., liver fibrosis or atherosclerotic plaques, demonstrating a possible use in several fibrotic organ systems, imaginable even in the same multimorbid patient (Ehling et al., 2013; Makowski et al., 2011; Megens et al., 2007).

4. New therapeutic options for fibrosis and CKD (994)

In 2017, we already discussed the interventional clinical studies of direct antifibrotic treatment in CKD patients. At that time, these comprised 17 trials focusing on the targets TGF-β, CTGF, integrin α5β6 and galectin-3, out of which six trials were either still running or completed but had not yet published their results (Klinkhammer et al., 2017). The *status quo* in 2023 is that still none of those trials has published results, even though all preclinical and translational analyses had shown very promising beneficial effects (Figure 2A) (Dang et al., 2012; Desmedt et al., 2016; Henderson et al., 2008; Kok et al., 2014; Okada et al., 2005; Wang et al., 2011; Yokoi et al., 2004). The only drug that seems to progress in translation is Pirfenidone. Still, there are no published results on the last phase 3 trial in DN patients (NCT02689778, 2016-2019), but a new study (NCT04258397, TOP-CKD) is currently recruiting (Table 2).

As in 2017, there are still no direct anti-fibrotic treatments for kidney patients. Here, we will briefly discuss the effects of the recently implemented sodium-glucose co-transporter 2 (SGLT2) inhibitors (SGLT2i named gliflozins or flozins) and the new clinical trials on anti-fibrotic targets currently underway.

A new class of glucose-lowering drugs used in diabetes, i.e., SGLT2i, showed prominent kidney protective properties and represents an important success in CKD treatment for

patients with DM (CREDENCE (Perkovic et al., 2019) or DERIVE (Fioretto et al., 2018)) or without DM (e.g., EMPA-KIDNEY (The et al., 2023), DAPA-CKD (Beernink et al., 2023; Heerspink et al., 2020) or DIAMOND (Brown et al., 2021; Cherney et al., 2020; Keener, 2023) (Supp. Table 1). Given these consistent positive results, the KDIGO has updated its recommendations on SGLT2 inhibition in CKD patients with DM and now recommends it as first-line drug therapy when eGFR ≥20 ml/min per 1.73 m^2 (Kidney Disease: Improving Global Outcomes Diabetes Work, 2022; Rossing et al., 2022). Likely, SGLT2i will become a standard of care in non-DM CKD as well. The beneficial effects of treatment with SGLT2i included slowing the decline of eGFR/progression of CKD, reducing the risk of ESKD and secondary cardiovascular events and preventing deaths. The exact mechanisms of SGLT2 inhibition in CKD are not yet fully understood and might be multifactorial, including hemodynamic and metabolic effects, or likely the combination thereof (Hatanaka et al., 2016; Lu et al., 2022; Tanaka et al., 2018; Vallon et al., 2013). Concerning kidney fibrosis, some preclinical animal studies reported no effects of SGLT2 inhibition or genetic deletion on kidney fibrosis, while others observed anti-fibrotic effects (Tauber et al., 2021; Vallon et al., 2013; Zhang et al., 2018). It seems likely that SGLT2i do not have direct anti-fibrotic effects, but their renoprotective effects might result in a secondary reduction of fibrosis. Future studies on novel anti-fibrotic drugs, will need to take this into account and assess the potential added value on top of the standard therapy in CKD including SGLTi.

Since 2017, there are only a few interventional clinical trials that analyzed the effects of treatments specifically on fibrosis (Table 2), albeit most of the tested treatments have no direct anti-fibrotic effects. Three phase 2 trials test the efficacy of autologous or allogeneic bone marrow-derived mesenchymal stromal cells (MSC) infusions in patients with diabetic nephropathy or CKD with less than 50% IF/TA, or transplant recipients. The aim is to reduce kidney damage and fibrosis through the MSC's paracrine immunomodulatory, pro-angiogenic, anti-apoptotic and anti-fibrotic functions (https://nephstrom.eu/)(Chen et al., 2023a; Reinders et al., 2014). Although there were several encouraging preclinical studies on MSC administration in AKI and CKD settings in the last 20 years, there were also some negative

preclinical reports on lack of efficacy or maldifferentiation (Klinkhammer et al., 2014; Kunter et al., 2007). Whether these approaches will be used clinically in the future remains to be seen. One trial with Acthar gels in APOL1- associated nephropathy was withdrawn. Other current or recently completed trials evaluating the anti-fibrotic effects of pentoxifylline, doxycycline, or hyperbaric oxygen therapy (HBOT) have not yet published their results (Table 2). Anti-inflammatory drugs are also tested for their anti-fibrotic effects, although these might be rather secondary indirect effects (Table 2). Kidney transplant recipients receiving three months the mTOR inhibitor everolimus with low tacrolimus had by trend reduced overall kidney fibrosis compared to full dose tacrolimus with mycophenolate (Taber et al., 2019). Spleen tyrosine kinase was suggested to represent a novel and selective therapeutic target for patients with IgA nephropathy, who exhibited increased glomerular expression and activation of the protein (McAdoo and Tam, 2018). Treatment with Fostamatinib, an oral prodrug spleen tyrosine kinase inhibitor, marginally reduced glomerulosclerosis and tubulointerstitial fibrosis IgA nephropathy patients (Table 2). In addition to the drug-based trials, there are also approaches to treat patients with low-energy ultrasound shockwave therapy (Table 2). The background is that low-intensity waves should stimulate mechanoreceptors in the kidney and thereby promote angiogenesis and tissue repair (Klomjit et al., 2020). Whether this also helps to reduce fibrosis, which might be viewed as a form of misguided wound-healing remains to be seen.

A retrospective analysis of inflammatory and fibrotic biomarkers in blood was done in patients included in the FIGARO-DKD study, i.e. patients with diabetic kidney disease (DKD) treated with the nonsteroidal mineralocorticoid receptor antagonist Finerenone (BAY94-8862). The study revealed that although TGF-β was significantly lower after the treatment, blood concentrations of collagen 1 remained similar (Pitt et al., 2021). However, this does currently not exclude a reduction in kidney fibrosis which was not analyzed (Table 2). Finerenone was previously shown to slow CKD progression and reduce the risk of cardiovascular events in patients with DM (Bakris et al., 2020; Pitt et al., 2021). Compared to steroidal mineralocorticoid receptor antagonists, Finerenone has a better safety profile, e.g., does not induce hyperkalemia, and another biodistribution, e.g., similar accumulation in the heart and kidney

(Haller et al., 2016). This makes Finerenone an example of CKD treatment that has a direct positive effect on several other organs. Particularly since CKD patients often also suffer from comorbidities such as cardiovascular complications, including fibrotic changes in the heart and vasculature, CKD is also considered a “systemic disease”, and an optimal anti-fibrotic drug for CKD should exert inter-organ effects (Zoccali et al., 2017). The research interest in inter-organ crosstalk is progressively rising, helping us to identify new relevant biomarkers and targets for kidney patients. Many preclinical and translational studies have already shown that several cellular and molecular fibrotic pathways are similar across organs, e.g., TGF-β, α5-containing integrins or the transcription factor c-JUN (Henderson et al., 2013; Jimenez-Uribe et al., 2021; Schreibing et al., 2023; Wernig et al., 2017). The concept of clinical trials focusing directly on intervention for two (or even more) organ systems is probably more difficult to implement, but it could show the systemic effects of therapy, potentially bringing further benefit for multimorbid CKD patients.

Table 2: Selected interventional clinical studies testing new therapies for CKD.

Search was performed on https://clinicaltrials.gov/ only including trials between 2016 and 2023. Each method is sorted by starting date.
ACEi = angiotensin converting Eenzyme inhibitor, ACR = albumin-to-creatinine ratio, α1M = alpha 1 micro-globulin, ARB = angiotensin II receptor blocker, BMI = body mass index, BMP-7 = bone morphogenetic protein-7, BP = blood pressure, CKD-EPI = chronic kidney disease epidemiology collaboration, Cr = creatinine, DKD = diabetic kidney disease, DM = diabetes mellitus, DMSA = dimercapto succinic acid, ECD = expanded criteria donor, EDTA = ethylenediaminetetraacetic acid, eGFR = estimated glomerular filtration rate, HLA = human leukocyte antigens, MCP-1 = monocyte chemoattractant protein-1, MRI = Magnetic Resonance Imaging, MSC = Mesenchymal stromal cells, NGAL = neutrophil gelatinase-associated lipocalin, PIIINP = Procollagen III aminoterminal peptide N, RRT = ,T2D = type 2 diabetes, TGF-β = transforming Growth Factor beta, uCTGF = urinary connective tissue growth factor, US = ultrasound, UTI = urinary tract infection.

Inter-vention/ drug	Official Title	Status	Phase, Sponsor	Key Inclusion Criteria	Primary Outcome Measures	Results	URL
Mesenchymal stromal cells (MSC)							
MSC	Safety and Efficacy Study of Mesenchymal Stem Cell in Treating Kidney Fibrosis	Unknown, started March 2018	Phase1+2, Nanjing Medical University	- Written informed consent. - Glomerular sclerosis ratio ≤ 50%. - Renal tubulointerstitial fibrosis ratio ≤ 50%. - Negative pregnancy test. Moderately active disease under standard treatment.	- BUN - Serum Cr - eGFR - Cystatin C - Urine protein [Time Frame: 24 months] - *among the secondary outcome parameters:* *The pathology decrease in grade of renal fibrosis*	-	https://clinicaltrials.gov/ct2/show/NCT03460223

MSC	NEPHSTROM for Diabetic Kidney Disease (NEPHSTROM)	Active, December 2017-December 2023	Phase1+2, Multicenter, Mario Negri Institute for Pharmacological Research	- Male and female ≥ 40 and <85 years old. - T2D for 3 or more years - Urinary albumin excretion (UAE) ≥ 60 µg/min (in a 24-h urine collection) and urine albumin-to-creatinine ratio (UACR) ≥ 88 mg/g (≥ 10 mg/mmol) (in a spot morning urine collection); - Estimated GFR (eGFR) 30-50 ml/min/1.73 m^2 by the CKD-EPI equation on 2 or more consecutive measurements at least 30 days apart within the past 6 months; - A documented decline of eGFR of ≥ -10ml/min/1.73 m^2 over the past 3 years or documented rate of eGFR decline of ≥ -5 ml/min/1.73 m^2 year based on 3 or more consecutive readings at least 90 days apart in the past 18 months; - Lack of suspicion of renal diagnosis other than DKD; - informed consent.	- Number and severity of all pre-specified infusion-associated events and the overall number and frequency of adverse events. [Time Frame: Changes from baseline to study completion, up to 18 months after cell or placebo infusion. - *among the secondary outcome parameters:* *Inflammation and fibrosis related soluble mediators (Blood and urine bio-chip-based multiplex assay)*	-	https://clinicaltrials.gov/ct2/show/NCT02585622 https://nephstrom.eu/
MSC	Mesenchymal Stromal Cell Therapy in Renal Recipients (MSCs)	Unknown, recruiting since 2014	Phase 2, Leiden University Medical Center	- Subject is willing to participate in the study, must be able to give informed consent and the consent must be obtained prior to any study procedure. - Recipients of a first kidney graft from a deceased, living-unrelated or non-HLA identical living related donor > 50 years of age. - Panel Reactive Antibodies (PRA) ≤ 10%. - Patients must be able to adhere to the study visit schedule and protocol requirements. - If female and of child-bearing age, subject must be non-pregnant, non-breastfeeding, and use adequate contraception.	- Fibrosis by quantitative Sirius Red scoring of MSC treated and untreated groups [Time Frame: at 6 months compared to 4 weeks post transplant]	-	https://clinicaltrials.gov/ct2/show/NCT02057965
Pirfenidone							
Pirfenidone	Trial of Pirfenidone to Prevent Progression in Chronic Kidney Disease (TOP-CKD)	Recruiting, started October 2020	Phase 2, Veterans Medical Research Foundation	- Patients with eGFR ≥20 ml/min/1.73m2 using the CKD-EPI Creatinine equation - 4 variable Kidney Failure Risk Equation (KFRE) 5 year risk score >1% - Age 21 years or older	- Change from baseline in kidney fibrosis assessed by DW-MRI - urinary markers of tubulo-interstitial fibrosis (α1M, PIIINP, MCP-1) [Time Frame: Baseline to Month 12]	-	https://clinicaltrials.gov/ct2/show/NCT04258397
Xanthin-derivate							
Pentoxifylline	Pentoxifylline Effect in Patients With Diabetic Nephropathy.(PENFOSIDINE STUDY) (PENFOSIDINE)	Recruiting, March 2018	Phase 4, Maria Eugenia Galván Plata	- CKD - Type 2 diabetes mellitus - Microalbuminuria - Proteinuria - Creatinine plasma clearance < of 60 mL / min.	- Change in GFR [Time frame: baseline, 6, 12, 18, 24 month] - *among the secondary outcome parameters:* *Change in fibrosis markers (Brain natriuretic peptide)*	-	https://clinicaltrials.gov/ct2/show/NCT03664414
Antibiotics							
Doxycycline	A Trial of Doxycycline in Renal Disease (ADORE)	Completed, 2016-2018	Phase 1, University of California, San Francisco	- CKD pre-dialysis (eGFR< 30 ml/min/1.73m2 not on dialysis) - local 415/650/510 area codes - primary language English or Spanish	- Serum markers of fibrosis: collagen type III amino-terminal propeptide (PIIINP), soluble suppression of tumorigenicity 2 (ST2) - Urinary markers of fibrosis: Urinary PIIINP, Urinary α1M [Time Frame: 3 months]	-	https://clinicaltrials.gov/ct2/show/NCT02753426
Mineralocorticoid receptor antagonist (MRA)							
Finerenone (BAY94-8862)	An add-on Study to the FIGARO-DKD Study Called FIGARO-BM to Learn About the Link Between Biomarkers (Substances in the Blood Used as Indicators of Biological Processes, Disease Processes or Responses to Medication) and Finerenone in FIGARO-DKD Participants (FIGARO-BM)	completed, August 2021-December 2021	Phase 2, Bayer	- only participants who were enrolled in the FIGARO-DKD study (NCT02545049) and had received up to 20 mg finerenone or placebo for ≥24 months - for each participant, pharmacokinetic (PK) plasma samples from Visit 3 and at least 2 other Visits (Visit 5, Visit 8, Visit 11) must be available on storage from the main study FIGARO-DKD.	- Change in plasma biomarker levels after 36 months (Visit 11) of treatment versus 4 months (Visit 3) of treatment in a set of 27 pre-defined biomarkers (primarily of biomarkers of inflammation and fibrosis which have been published previously in the context of inflammation-related fibrosis and CKD) [Time Frame: 4 months and 36 months]	MMP7 was sign. higher, TGB-β, was sign. lower, while Col.1 and MMP9 was not changed https://www.clinicaltrials.gov/ct2/show/results/NCT05013008	https://www.clinicaltrials.gov/ct2/show/NCT05013008

Anti-inflammatory or immunosuppressive							
Fingolimod	Fingolimod for the Abrogation of Interstitial Fibrosis and Tubular Atrophy Following Kidney Transplantation	Not yet recruiting, March 2022	Phase 2, The Methodist Hospital Research Institute	- signed and dated informed consent form - Stated willingness to comply with all study procedures and availability for the duration of the study - Receiving a first or second kidney transplant - Male or female, aged ≥18 to ≤65 - Women of child bearing potential who have a negative serum pregnancy test prior to treatment - Women of child bearing potential (including perimenopausal women who have had a menstrual period within the previous 1 year) who agree to use 2 forms of effective birth control regimen (at least one of which is a barrier method) throughout the study period and for 6 weeks following the end of the study or the last dose of mycophenolic acid, whichever comes first. - Panel of reactive antibodies <50% - Able to take oral medication - Agreement to adhere to Lifestyle Considerations throughout study duration: refraining from the consumption of grapefruit or grapefruit juice and stopping any anticoagulation therapy, including ASA, one week prior and one week post kidney biopsy procedure	- Emergent and Adverse Events [Time Frame: Baseline (day of kidney transplant surgery); 3, 14, 30, 90, 180, 270, and 365 days after starting study drug or placebo] - *among the secondary outcome parameters: Procollagen 3 Peptide, BMP-7, TGF-beta*	-	https://clinicaltrials.gov/ct2/show/NCT05285878
Everolimus	Novartis Everolimus Transition	Completed, 2014-2018	Phase 4, Medical University of South Carolina	- At least 18 years of age and able to give informed consent. - Received a first or repeat cadaveric (including ECD) or living donor renal transplant - Patient has stable graft function, defined as no change of greater than 40% of baseline serum creatinine and no acute rejection during the past month. - Currently receiving tacrolimus, mycophenolate mofetil and prednisone as their immunosuppression regimen	- Kidney Allograft Fibrosis Assessment [Time Frame: 1 year]	(Taber et al., 2019)	https://clinicaltrials.gov/ct2/show/NCT02096107
Fostamatinib	Safety and Efficacy Study of Fostamatinib to Treat Immunoglobin A (IgA) Nephropathy	Completed, October 2014-March 2018	Rigel Pharmaceuticals	- Renal biopsy findings consistent with IgA nephropathy - Treatment with an Angiotensin Converting Enzyme inhibitor (ACEi) and/or an Angiotensin II Receptor Blocker (ARB) for at least 90 days at the maximum approved (or tolerated) dose - Proteinuria > 1 gm/day at diagnosis of IgA nephropathy and Proteinuria > 0.50 gm/day at the second Screening Visit - Blood pressure controlled to ≤ 130/80 with angiotensin blockade with or without other anti-hypertensive agents	- Mean Change of Proteinuria as Measured by Spot Urine Protein/Creatinine Ratio (sPCR) at Week 24 [Time Frame: Baseline to 24 weeks] - *among the secondary outcome parameters: Percentage of Glomeruli With Segmental Sclerosis/Adhesion or Global Glomerulosclerosis; Percentage of Tubulointerstitial Scarring*	No sign. change in MEST-C scores. https://clinicaltrials.gov/ct2/show/results/NCT02112838	https://clinicaltrials.gov/ct2/show/NCT02112838
Adrenocorticotropic hormone							
Acthar	ACTH Treatment of APOL1-Associated Nephropathy	Withdrawn, January 2014-January 2019	Wake Forest University Health Sciences	- Non-diabetic African-American with two APOL1-risk genotypes - Age ≥21 years - BMI < 40 kg/m2 - Hemoglobin A1c <6.5% - eGFR ≥30 ml/min/1.73m2 - Historical urine protein: creatinine ratio ≥ 1.0 g/g - Strong clinical suspicion of APOL1-associated nephropathy or history of biopsy proven focal segmental glomerulosclerosis (FSGS) or focal global glomerulosclerosis (FGGS) - Women of childbearing potential: negative serum pregnancy test at Screening and agreement to follow a medically acceptable form of contraception for the duration of Acthar administration and 4 weeks thereafter	- Change in proteinuria with H.C. Acthar gel - Change in eGFR with H.C. Acthar gel [Time Frame: End of treatment with H.C. Acthar gel (end of 6 months or 1 year of treatment)] - *among the secondary outcome parameters: Changes in kidney fibrosis after H.C. Acthar gel treatment (kidney histopathology on second post-treatment kidney biopsy (% glomerulosclerosis, % tubulointerstitial fibrosis, restoration of podocyte markers) compared with baseline biopsy)*	n.a.	https://clinicaltrials.gov/ct2/show/NCT02006849
Oxygen							
Hyperbaric oxygen therapy (HBOT)	Hyperbaric Oxygen Therapy for Renal Regeneration in Diabetic Nephropathy	Unknown (started January 2016)	Phase 2, Assaf-Harofeh Medical Center	- 18 years or older - DKD, defined as eGFR<60ml/min as estimated using MDRD formula, and albuminuria in the presence of diabetes. - Diabetic retinopathy - without any alternative cause for their renal disease	- GFR - Proteinuria [Time Frame: 1 month after treatment] - *among the secondary outcome parameters: fibrosis (DWI MRI)*	-	https://www.clinicaltrials.gov/ct2/show/NCT03376282
Ultrasound							

Low-energy extracorporeal ultrasound shockwave therapy (SWT)	Ultrasound Wave Therapy for Post-stenotic Microvascular Remodeling	Not yet recruiting, start March 2023	Mayo Clinic	- Patients are between ages 40 and 80 years old. - Patients with hypertension (Systolic BP> 155 mm Hg) and/or requirement for two or more antihypertensive medications for more than 4 weeks, no restrictions on antihypertensive agents, although loop diuretics may be changed to diluting site agents (e.g. hydrochlorothiazide, indapamide, metolazone) for two weeks prior to study. - Patients have serum creatinine ≤2.2 mg/dL. - Patients have no contraindications to angiography: severe contrast allergy. - Patients have no contraindications to no-contrast MR evaluations: e.g., pacemaker or magnetically active metal fragments, claustrophobia. - Patients have the ability to comply with protocol - Written informed consent	- Change in kidney perfusion - Change in eGFR - Change in blood oxygen in kidney assessed by MRI - Change in renal fibrosis assessed by MRI - Change in urinary levels of biomarkers and extracellular vehicles - Change in labs collected from right and left renal veins and/or Inferior Vena Cava - Change in mean arterial pressure assessed by oscillometry - Change in peripheral microvascular endothelial function assessed in the fingertip [Time Frame: Baseline, 3 months]	-	https://clinicaltrials.gov/ct2/show/NCT03914157
Low energy shockwave therapy	Low Energy Shockwave Therapy (LE-SWT): A Novel Treatment for Chronic Kidney Disease	Unknown, July 2015-January 2022	Odense University Hospital	CKD stage 3: Moderate reduction in GFR in patients with diabetes mellitus (DM)	- Chromium-EDTA clearance - Histological assessment of endothelial growth in kidneys - Nitrite, nitrate and cGMP concentrations in spot urine sample (composite outcome) - NGAL concentration in spot urine sample. - Patient-reported quality of life - Histological assessment of fibrosis in kidney biopsy - Changes in glomerulus basal lamina assessed using transmission electron microscopy [Time Frame for all points: 19 months after enrollment] - Albumin/creatinine ratio in spot urine sample [Time Frame: 2 months after enrollment]	-	https://clinicaltrials.gov/ct2/show/NCT02515461

5. Novel approaches and future perspectives (1080)

Recent advances in high-throughput omics technologies, such as proteomics, metabolomics, (epi)genomics and transcriptomics, led to a transformation in kidney research and have extended our knowledge on kidney diseases accelerating the identification of molecular pathways, novel potential biomarkers and treatment targets for kidney fibrosis (Dubin and Rhee, 2020; Saez-Rodriguez et al., 2019). We here discuss some major examples of recent findings in kidney fibrosis using these methods.

Proteomic analysis of specimens with different forms of idiopathic glomerulonephritis by MALDI mass spectrometry identified α-1-antitrypsin as a podocyte stress and CKD progression marker in focal segmental glomerulosclerosis (FSGS), measurable in tissue and urinary specimen (Smith et al., 2016). A currently recruiting clinical trial “Proteogenomic Monitoring and Assessment of Kidney Transplant Recipients”

(https://clinicaltrials.gov/ct2/show/NCT01531257) also aims to correlate blood and urine profiles with an extra core biopsy, to validate specific proteogenomic biomarker panels for fibrosis in chronic allograft nephropathy. Mass spectrometric urine proteomics from patients with IgAN also identified α-1-antitrypsin and various collagen peptides as predictors for disease progression which were further confirmed in another study by proteomic profiling of IgAN biopsies (Chen et al., 2023b; Rudnicki et al., 2021).

Focusing on the transcriptomic level, a meta-analysis of genome-wide association studies (GWAS) including ca. 27,000 DKD patients, showed that tubular doublecortin-like kinase 1 (DCLK1) was associated with ESKD, strongly correlated with the extent of fibrosis and might be involved in the pathogenesis of DKD (Sandholm et al., 2022). Another GWAS identified the COL4A3 locus, encoding the ECM protein collagen 4, to have a strong association with DKD, which is surprising since mutations in this gene cause the progressive inherited nephropathy Alport syndrome (Salem et al., 2019). In transplant kidneys with allograft fibrosis, single-cell transcriptomics identified three distinct stromal cell clusters including RSG+CACNA1C+ pericytes, MOXD1+ fibroblasts and COL8A1+COL12A1+ myofibroblasts (Wu et al., 2018). With a different set of marker genes, another study identified four subclusters of fibroblasts in transplant kidneys and found in gender-mismatched grafts that most of these fibroblasts were of recipient origin, similar to immune cells (Suryawanshi et al., 2022). Using single-cell RNA sequencing, spatial transcriptomics, and assay for transposase-accessible chromatin using (ATAC) sequencing a recent comprehensive study identified three distinct subpopulations of cells, i.e., pericytes (NOTCH3+RGS5+PDGFRA-), MEG3+PDGFRα+ and COLEC11+CXCL12+ fibroblasts, to be the main cellular sources of scar-forming myofibroblasts (PDGFRA+, PDGFRB+, POSTN+) to during human kidney fibrosis (Kuppe et al., 2021). The study also found the protein naked cuticle 2 (NKD2), a modulator of the Wnt signaling, to be expressed by the ECM-producing myofibroblasts in mice and humans. NKD2 was suggested as a novel potential therapeutic target given that the functional overexpression increased ECM production and the knockout significantly decreased fibrosis (Kuppe et al., 2021). The same authors also showed that Runx1 is crucially involved in the differentiation of

myofibroblasts and upregulated TGF-β receptor and ECM proteins thereby driving fibrosis (Li et al., 2021b).

A combination of omics techniques even provides deeper insights into cell interactions, pathomechanisms and tissue dynamics and thus might help to identify the best target for therapeutic interventions (Longo et al., 2021). By combining DNA methylation, microRNA and gene expression analyses in allograft biopsies, one study found that the expression of only three miRNAs was regulated by DNA methylation in fibrosis. However, these three miRNAs were, among others, important regulators of the TGF-β signaling pathway (Bontha et al., 2017). The current advances in big data generation require novel developments in the field of computational data integration and analyses (Saez-Rodriguez et al., 2019). Initially, some web applications offered access and basic analysis of multi-omics-data, e.g., the Kidney and Urinary Pathway Knowledge Base (KUPKB) or the Mouse Kidney Fibromics browser (proteomics, mRNA and small RNA transcriptomics from murine UUO and folic acid fibrosis models), but, to our knowledge, both are not available anymore in 2023 (Klein et al., 2012; Pavkovic et al., 2019). Now, more efforts are made to generate and bring together data and interdisciplinary specialists through large-scale projects. Examples of such consortia are, e.g., The George M. O'Brien Michigan Kidney Translational Core Center (https://kidneycenter.med.umich.edu/) or the Clinical Research Unit CRU5011 (https://www.interakd.de/) which sometimes offer also open source interactive plattforms focussing on kidney diseases, such as the Kidney Precision Medicine project (KPMP, https://atlas.kpmp.org/), or nephrocell and nephroseq (http://nephrocell.miktmc.org/ https://nephroseq.org/), and fibrosis, e.g. FibROAD (https://www.fibroad.org/) (Bitzer et al., 2022; de Boer et al., 2021; Ong et al., 2020; Sun et al., 2022). These projects bring together both data and the expertise of different disciplines and experts, facilitating translational research in kidney fibrosis. Open source provision of generated, quality-assured data to the community, ensures better transparency in research, accelerates the dissemination and establishment of new findings, and simplifies the verification of new results.

High-throughput digitalization of pathological slides using slide scanners, i.e., digital pathology, opens new possibilities for automated, highly precise, and reproducible quantifications in (nephro)pathology (Barisoni et al., 2017; Barisoni and Hodgin, 2017; Becker et al., 2020; Boor, 2020). Kidney fibrosis itself can be automatically analyzed with a machine and deep learning without the need for specific histological or immunostains (Liu et al., 2022b; Marechal et al., 2022; Tey et al., 2018; Zheng et al., 2021). Many approaches use segmentation tools to automatically and virtually dissect the kidney histology in its different compartments, e.g., glomeruli, tubules, vessels and interstitium, or even single cells to extract information from each unit. A recent publication extracted around 40 million quantitative morphometric data from 1043 non-tumor kidney histologies and applied bioinformatic techniques from single-cell transcriptomics identifying distinct glomerular populations and morphometric phenotypes along a trajectory of disease progression ending in complete glomerulosclerosis. This novel omics field named “pathomics” will likely complement the methodological armamentarium to study fibrosis, e.g., defining in large-scale location, distribution or composition of the ECM (Holscher et al., 2023).

In addition to clinical trials and human data, nephrology research still profits from preclinical animal studies. Complex fibrosis cannot yet be exclusively mimicked *ex vivo*, e.g., in organoid or 3D cell cultures or with *in silico* simulations. There are several animal models of kidney fibrosis, e.g., the surgical models of unilateral ureteral obstruction (UUO), ischemia-reperfusion injury (IRI) and 5/6 nephrectomy, the toxicity models of aristolochic acid and folic acid nephropathy and crystal-induced models of adenine nephropathy (Djudjaj and Boor, 2019; Kramann and Menzel, 2021). Despite various promising data from animal studies that have investigated anti-fibrotic treatments in CKD models, there was no successful translation into the clinic (Figure 2B) (Djudjaj and Boor, 2019). To optimize the models and to obtain the greatest possible insight and benefit for translation, the first consensus paper on "guidance for preclinical animal studies in translational nephrology" was published by the International Society of Nephrology (Nangaku et al., 2023). In addition to the ARRIVE guidelines for reporting animal research, the new recommendations specifically tackle kidney models and,

e.g., guide how to select the most suitable model, organism, controls and group size, emphasize pharmacokinetic studies in healthy animals, suggest performing interventional treatments only in established disease, and provide recommendations how to evaluate and report results (Kilkenny et al., 2010; Nangaku et al., 2023). This should make the results more comparable and also give them a higher translational value. The adoption of such recommendations by scientific journals could strongly facilitate the value of preclinical studies and potentially improve the translational landscape in nephrology.

6. Conclusion (123)

Despite the increasing number of patients with CKD and kidney fibrosis, no antifibrotic treatments and no non-invasive fibrosis-specific diagnostics exist. The translation is still slow and lags behind other disciplines. Some successes in CKD treatment and promising studies in diagnostics provide important stimuli for further research. The advancement of novel technologies, particularly of single-cell and spatially resolved multi-omics, holds great potential for a better understanding of the underlying mechanisms of kidney fibrosis and the identification of novel biomarkers and treatment targets. Intensified fibrosis research across organs holds great potential to identify overarching vs. organ-specific concepts, both of which could be exploited for therapies and diagnostics. Altogether, kidney fibrosis remains an exciting area of research with immense potential for the majority of kidney patients.

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FIGURES

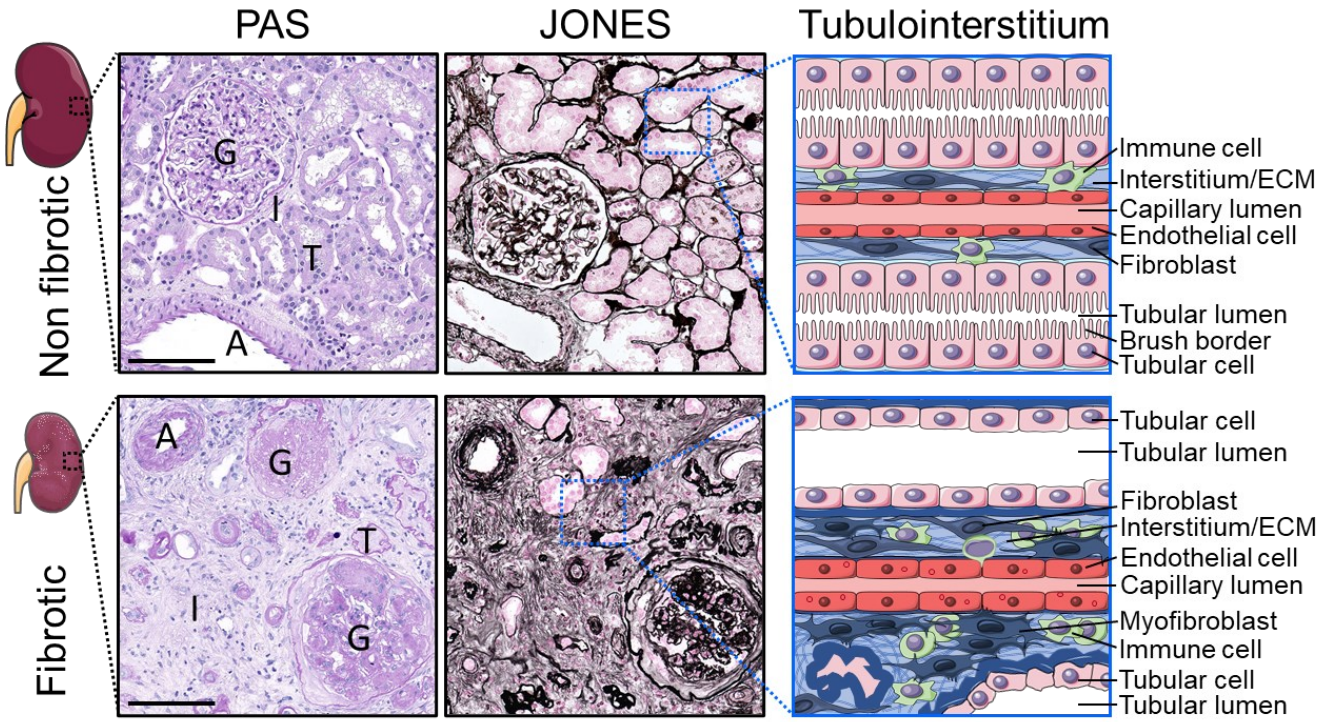


Figure 1: Morphological differences between healthy and fibrotic kidneys.

Shown are kidney images from two histological stains, i.e., PAS, showing kidney morphology, and JONES, staining basement menbranes and ECM in black, and a schematic illustration of the tubulointerstitial space in healthy and fibrotic kidneys. The upper panel shows healthy kidneys and the scheme of healthy tubulointerstitial space comprising tubules, capillaries and the interstitium with a few resident immune cells and fibroblasts. The lower panel shows images from a fibrotic kidney. Glomeruli (G) are sclerotic and also the artery (A) shows more collagen deposition. Tubules (T) show sign of injury, e.g. dilation and loss of brush border, and atrophy with shrunken size and irregular and thickended basement membrane. The interstitium (I) has massively expanded and shows more immune cells and a high accumulation of mesenchymal cells, e.g., fibroblasts and myofibroblasts, producing high amount of ECM components. A = Artery, ECM = extracellular matrix, G = Glomerulus. Scale bar = 100 µm.

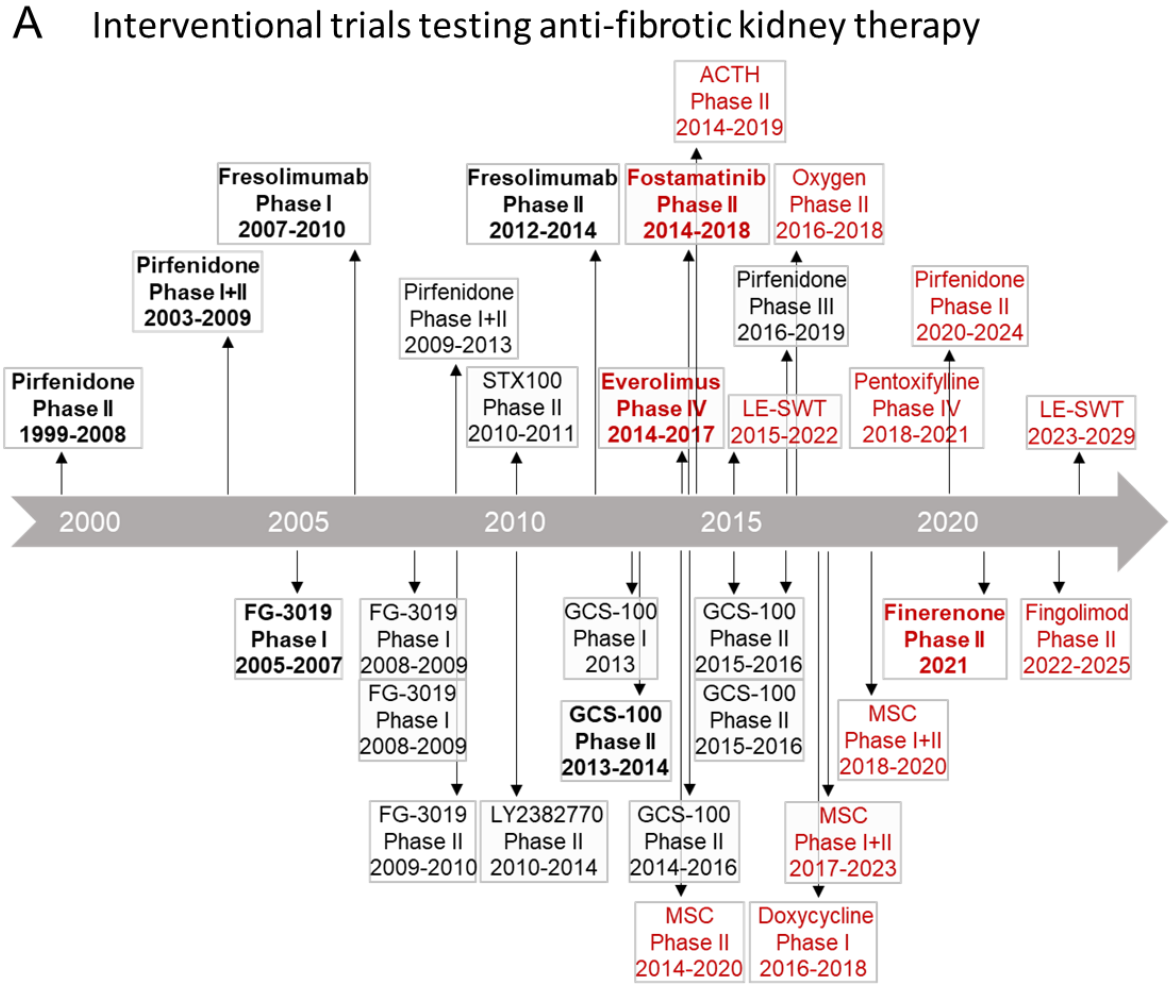


Figure 2: Development of research and clinical trials in kidney fibrosis.

A) Time line of interventional clinical trials testing direct and indirect anti-fibrotic agents in kidney diseases. Trials in black were discussed previously in (Klinkhammer et al., 2017) and trials in red are discussed in the current review. Trials with published results are shown in bold. B) Pubmed literature research records for kidney fibrosis related topics. While the number of

studies focusing on kidney fibrosis is progressively increasing per year, the number of clinical trials related to kidney fibrosis stays consistently low with no discernible trend.

ACTH = Acthar gel, FG-3019 = Human monoclonal antibody against connective tissue growth factor, Fresolimumab = human monoclonal antibody against TGF-β, GCS100 = galectin-3 antagonist, LE-SWT = Low energy shockwave therapy, LY2382770 = humanized anti-TGF-β antibody, MSC = mesenchymal stromal cell

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SUPPLEMENT (If possible)

Supp. Table 1: Interventional clinical studies testing SGLT2 inhibition as therapy for CKD patients

Search only included trials between 2016 and 2023.

T2DM (Type 2 diabetes mellitus), eGFR (estimated glomerular filtration rate)

Intervention /Drug	Title	Status	Phase, Sponsor	URL
Canagliflozin				
Cana	Safety and Efficacy of Canagliflozin in Advanced CKD (SIP-AKiD)	Recruiting, Since November 2022	Phase 4, McGill University Health Centre/Research Institute of the McGill University Health Centre	https://clinicaltrials.gov/ct2/show/NCT05309785
Cana	A Randomized, Double-blind, Event-driven, Placebo-controlled, Multicenter Study of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Subjects With Type 2 Diabetes Mellitus and Diabetic Nephropathy (CREDENCE)	Completed, February 2014-October 2018	Phase 3, Janssen Research & Development, LLC	https://clinicaltrials.gov/ct2/show/NCT02065791
Dapagliflozin				
Dapa	Effect of SGLT2i on Cardiovascular Biomarkers in Patients With Type 2 Diabetes and CKD Stage 3b-4	Recruiting, since November 2022	Phase 1, University of Texas Southwestern Medical Center	https://clinicaltrials.gov/ct2/show/NCT05033054
Dapa	A Randomized Controlled Clinical Trial to Assess the Effect of Dapagliflozin on Renal and Cardiovascular Outcomes in Patients With Severe Chronic Kidney Disease (The RENAL LIFECYCLE Trial)	Enrolling by invitation, since November 2022	Phase 3, University Medical Center Groningen	https://clinicaltrials.gov/ct2/show/NCT05374291
Dapa	SGLT2 Inhibition (Dapagliflozin) in Diabetic and Non-diabetic Hemodialysis Patients With and Without Residual Urine Volume: a Prospective Randomized, Placebo-controlled, Double-blinded Phase II Trial (DAPA-HD)	Recruiting, Since October 2022	Phase 2, Medical University of Vienna	https://clinicaltrials.gov/ct2/show/NCT05179668
Dapa	A 6-Month, Randomized, Double-Blind Study to Evaluate the Effect of Dapagliflozin on EChOcardiographic Measures of CarDiac StructurE and Function in Patients With Chronic Kidney Disease (DECODE-CKD)	Recruiting, since June 2022	Phase 2, Tor Biering-Sørensen	https://clinicaltrials.gov/ct2/show/NCT05359263
Dapa	Efficacy and Safety of Dapagliflozin in Patients With Chronic Kidney Disease Stage 4-5 Under Integrated CKD Care Program: An Investigator-led, Randomized, Open-label, Blinded-endpoint, Multicenter Study (DAPA-advKD)	Not yet recruiting, since March 2022	Phase 3, Kaohsiung Medical University	https://clinicaltrials.gov/ct2/show/NCT05196347
Dapa	Effect of Short-term Dapagliflozin on Renal Function After Heart Catheterization or Percutaneous Coronary Intervention in Patients With Chronic Kidney Disease	Recruiting, Since January 2022	Phase 4, Dong-A University	https://clinicaltrials.gov/ct2/show/NCT05225077
Dapa	Dapagliflozin Effect on Cardiovascular Outcomes in Haemodialysis for End Stage Renal Disease (DECODED)	Not yet recruiting, started February 2021	Phase2+3, Tan Tock Seng Hospital	https://clinicaltrials.gov/ct2/show/NCT04764097
Dapa	Evaluating the Short-term Renal and Systemic Effects of Dapagliflozin in Non-diabetic Patients With Stage IV CKD at Risk of ESKD Because of Severe Renal Insufficiency and Persistent Proteinuria: A Prospective, Randomized, Double-blind, Placebo-controlled, Cross-over Study (ADAPT)	Recruiting, since October 2021	Phase 2, Mario Negri Institute for Pharmacological Research	https://clinicaltrials.gov/ct2/show/NCT04794517
Dapa	Impact of Dapagliflozin on Vascular Function in Chronic Kidney Disease Patients (DAPAVASC)	Active, since December 2021	Phase 2, University Hospital, Rouen	https://clinicaltrials.gov/ct2/show/NCT04930549
Dapa	A Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients With Chronic Kidney Disease (Dapa-CKD)	Completed, February 2017-June 2020	Phase 3, AstraZeneca	https://clinicaltrials.gov/ct2/show/NCT03036150
Dapa	A Study to Assess the Renoprotective Effects of the SGLT2 Inhibitor Dapagliflozin in Non-Diabetic Patients With Proteinuria: a Randomized Double Blind 6-Weeks Cross-Over Trial (DIAMOND)	Unknown, Since November 2017 (-December 2019)	Phase 2, Hiddo Lambers Heerspink	https://clinicaltrials.gov/ct2/show/NCT03190694
Dapa	Treating to Reduce Albuminuria and Normalize Hemodynamic Function in Focal ScLerosis With dApagliflozin Trial Effects: "The TRANSLATE Study"	Completed, September 2015 – April 2017	Phase 4, University Health Network, Toronto	https://clinicaltrials.gov/ct2/show/NCT02585804

Dapa	A Multicenter, Double-Blind, Placebo-Controlled, Parallel Group, Randomized, Phase III Study to Evaluate the Glycemic Efficacy and Renal Safety of Dapagliflozin in Patients With Type 2 Diabetes Mellitus and Moderate Renal Impairment (CKD 3A) Who Have Inadequate Glycemic Control (DERIVE)	Completed, June 2015-November 2017	Phase 3, AstraZeneca	https://clinicaltrials.gov/ct2/show/NCT02413398
Dapa + Zibotentan	A Study to Assess the Effects of the Endothelin Receptor Antagonist Zibotentan and the SGLT2 Inhibitor Dapagliflozin in Patients With Type 2 Diabetes and Elevated Albuminuria: a Randomized Double Blind Cross-Over Trial (ZODIAC)	Enrolling by invitation, Since October 2022	Phase 2, University Medical Center Groningen	https://clinicaltrials.gov/ct2/show/NCT05570305
Dapa + Zibotentan	A Phase 2b Multicentre, Randomised, Double-Blind, Active-Controlled, Parallel Group Dose-Ranging Study to Assess the Efficacy, Safety and Tolerability of Zibotentan and Dapagliflozin in Patients With Chronic Kidney Disease With Estimated Glomerular Filtration Rate (eGFR) ≥ 20 mL/Min/1.73 m^2 (ZENITH-CKD)	Recruiting, since April 2021	Phase 2, AstraZeneca	https://clinicaltrials.gov/ct2/show/NCT04724837
Dapa + Zibotentan	A Phase 1, Open-label Study With Two Independent Parts: Collecting Samples for Metabolites in Safety Testing Analysis of Zibotentan After Repeated Administration (Part 1); and a Randomised, Cross-over, Three Period, Three-treatment, Single Dose Study to Assess the Relative Bioavailability of Different Formulations of Zibotentan and Dapagliflozin (Part 2) in Healthy Adult Participants	Completed, July 2021 - October 2021	Phase 1, AstraZeneca	https://clinicaltrials.gov/ct2/show/NCT04991571
Dapa + Saxagliptin	An Exploratory Phase II/III, Randomized, Double-blind, Placebo Controlled, Parallel Design Study to Evaluate the Efficacy, Safety and Pharmacodynamics of Dapagliflozin and Dapagliflozin in Combination With Saxagliptin in CKD Patients With Type 2 Diabetes Mellitus and Albuminuria Treated With ACEi or ARB (DELIGHT)	Completed, September 2015 – May 2018	Phase 2+3, AstraZeneca	https://clinicaltrials.gov/ct2/show/NCT02547935
Dapa (+ACEI)	Efficacy and Safety of Dapagliflozin in Children With Proteinuric Chronic Kidney Disease : a Prospective, Randomized, Placebo-controlled Trial	Withdrawn (lack of funding)	Phase 4, Children's Hospital of Fudan University	https://clinicaltrials.gov/ct2/show/NCT04531397
Dapa vs. Huangqi Guizhi Wuwu decoction	A Prospective, Open, Multicenter, Clinical Study of Huangqi Guizhi Wuwu Decoction in Treating Diabetic Nephropathy (Stage CKD2-4)	Recruiting, Since January 2022	The First Affiliated Hospital of Dalian Medical University	https://clinicaltrials.gov/ct2/show/NCT05418465
Dapa + AZD5718	A Phase 2b Randomised, Double-Blind, Placebo-Controlled, Multi-Centre, Dose-Ranging Study of AZD5718 in Participants With Proteinuric Chronic Kidney Disease (FLAIR)	Completed, October 2020 – September 2022	Phase 2, AstraZeneca	https://clinicaltrials.gov/ct2/show/NCT04492722
Dapa + AZD9977	A Phase 2b, Randomised, Double-Blind, Active Controlled, Multi Centre Study to Evaluate the Efficacy, Safety and Tolerability of Oral AZD9977 and Dapagliflozin Treatment in Patients With Heart Failure and Chronic Kidney Disease (MIRACLE)	Recruiting,	Phase 2, AstraZeneca	https://clinicaltrials.gov/ct2/show/NCT04595370
Empagliflozin				
Empa	Empagliflozin for Patients With Acutely Decompensated Congestive Heart Failure, Diuretic Resistance, and Moderate to Advanced Chronic Kidney Disease	Recruiting, Since December 2022	Phase 4, McGill University Health Centre/Research Institute of the McGill University Health Centre	https://clinicaltrials.gov/ct2/show/NCT05305495
Empa	Evaluating the Short-Term Renal and Systemic Effects of SGLT2 Inhibition in Non-Diabetic Patients at Risk of Accelerated GFR Decline Because of Glomerular Hyperfiltration: a Sequential OFF-ON-OFF Study With One-Month Empagliflozin Therapy Followed by One-Month Recovery Period (EMPATHY)	Withdrawn (Lack of funds), September 2021	Phase 2, Mario Negri Institute for Pharmacological Research	https://clinicaltrials.gov/ct2/show/NCT04143581
Empa	A Multicentre International Randomized Parallel Group Double-blind Placebo-controlled Clinical Trial of EMPAgliflozin Once Daily to Assess Cardio-renal Outcomes in Patients With Chronic KIDNEY Disease (EMPA-KIDNEY)	Active, not recruiting, Since January 2021	Phase 3, Boehringer Ingelheim	https://clinicaltrials.gov/ct2/show/NCT03594110
Empa	Effect of Sodium Glucose co Transporter 2 (SGLT2) Inhibition on Optical Coherence Tomography Angiography (OCT-A) Parameters in Diabetic Chronic Kidney Disease (CKD)	Unknown, started May 2020	Phase 4, National University of Malaysia	https://clinicaltrials.gov/ct2/show/NCT04215445
Empa	Effect of Empagliflozin on Urinary Excretion of Adenosine and on Markers of Osteocyte Function and Glomerular Damage in Diabetic and Non-diabetic Patients With Chronic Kidney Disease	Recruiting, Since January 2019	Phase 2-3?, Medical University of Lodz	https://clinicaltrials.gov/ct2/show/NCT04961931
Empa	A Single-center, Prospective, Placebo-controlled, Double-blind, Randomized, Cross-over Mechanistic Intervention Study to Investigate the Effect of Empagliflozin on Kidney Function in People With Either Preserved or Impaired Kidney Function With or Without Type 2 Diabetes (REGROUP)	Withdrawn (COVID), July 2020-March 2022	Phase 4, Amsterdam UMC, location VUmc	https://clinicaltrials.gov/ct2/show/NCT04243850

Empa	Effect of Empagliflozin on the Renin-angiotensin System in Patients With Chronic Kidney Disease (EMPRA)	Completed, April 2017 – August 2019	Phase 2, Medical University of Vienna	https://clinicaltrials.gov/ct2/show/NCT03078101
Empa + Metformin	Clinical Study Evaluating the Efficacy and Safety of Metformin Versus Empagliflozin for Halting Chronic Kidney Disease Progression	Recruiting, since January 2022	Phase 2-3, Tanta University	https://clinicaltrials.gov/ct2/show/NCT05373680
Empa + Finerenone	A Parallel-group Treatment, Phase 2, Double-blind, Three-arm Study to Assess Efficacy and Safety of Finerenone Plus Empagliflozin Compared With Either Finerenone or Empagliflozin in Participants With Chronic Kidney Disease and Type 2 Diabetes (CONFIDENCE)	Recruiting, Since June 2022	Phase 2, Bayer	https://clinicaltrials.gov/ct2/show/NCT05254002
BI 690517 + Empa	Randomised, Double-blind, Placebo-controlled and Parallel Dose Group Trial to Investigate Efficacy and Safety of Multiple Doses of Oral BI 690517 Over 14 Weeks, Alone and in Combination With Empagliflozin, in Patients With Diabetic and Non-diabetic Chronic Kidney Disease	Recruiting, since January 2022	Phase 2, Boehringer Ingelheim	https://clinicaltrials.gov/ct2/show/NCT05182840
Ertugliflozin				
Ertu	A Phase III, Multicenter, Randomized, Double-Blind, Placebo-Controlled Clinical Trial to Evaluate the Efficacy and Safety of Ertugliflozin (MK-8835/PF-04971729) in Subjects With Type 2 Diabetes Mellitus With Stage 3 Chronic Kidney Disease Who Have Inadequate Glycemic Control on Background Antihyperglycemic Therapy (MK-8835-001)	Completed, December 2013 – September 2016	Phase 3, Merck Sharp & Dohme LLC	https://clinicaltrials.gov/ct2/show/NCT01986855
Sotagliflozin				
Sota	A Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Demonstrate the Effects of Sotagliflozin on Cardiovascular and Renal Events in Patients With Type 2 Diabetes, Cardiovascular Risk Factors and Moderately Impaired Renal Function (SCORED)	Terminated (study terminated due to business decision), December 2017-July 2020	Phase 3, Lexicon Pharmaceuticals	https://clinicaltrials.gov/ct2/show/NCT03315143
Sota	A Randomized, Double-blind, Placebo-controlled, 3-arm, Parallel-group 52-week Multicenter Study to Evaluate the Efficacy and Safety of Sotagliflozin in Patients With Type 2 Diabetes Mellitus and Moderate Renal Impairment Who Have Inadequate Glycemic Control (SOTA-CKD3)	Completed, August 2017 - March 2019	Phase 3, Lexicon Pharmaceuticals	https://clinicaltrials.gov/ct2/show/NCT03242252
Sota	A Randomized, Double-blind, Placebo-controlled, 3-arm, Parallel-group 52-week Multicenter Study to Evaluate the Efficacy and Safety of Sotagliflozin in Patients With Type 2 Diabetes Mellitus and Severe Renal Impairment Who Have Inadequate Glycemic Control (SOTA-CKD4)	Completed, August 2017 - May 2019	Phase 3, Lexicon Pharmaceuticals	https://clinicaltrials.gov/ct2/show/NCT03242018