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1. PATHOPHYSIOLOGY AND CLASSIFICATION OF KIDNEY DISEASES

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1.1 Classification of CKD

Chronic kidney disease (CKD) is far more prevalent worldwide than was previously assumed. It affects 10 - 15% of the adult population in the western countries, many of whom require costly treatments or renal replacement therapy. According to the Third National Health and Nutrition Examination Survey and the National Kidney Foundation Kidney Disease report nearly 26 million persons in the USA fall into this category and another 20 millions are at an increased risk for CKD. Moreover, it has been recognized that CKD is a major risk factor for increased cardiovascular disease and death. This knowledge has been incorporated in the recent cardiologic guidelines as well as in the 2007 European Guidelines for the Management of Arterial Hypertension. At the same time, there is an increasing prevalence of diseases that predispose individuals to CKD, such as hypertension, diabetes, obesity and other, rendering the prevention and early detection of CKD a health-care priority in both developed and developing countries.

In 2002 the Kidney Disease Outcomes Quality Initiative (K/DOQI) of the National Kidney Foundation has published guidelines to define CKD and to classify stages in its progression. This classification system is based on the level of kidney function as estimated by glomerular filtration rate (GFR) regardless of the underlying pathology. Subsequent interventional guidelines, specific to each of these stages, have been published on dyslipidemia, bone mineral metabolism and disease, and blood pressure. In 2004 the international organization Kidney Disease: Improving Global Outcomes (KDIGO), governed by an international board of directors, was formed to address the worldwide epidemic of CKD by facilitating the development and implementation of the guidelines with a stated mission to "improve the care and outcomes of kidney disease patients worldwide through promoting coordination, collaboration and integration of initiatives to develop and implement clinical practice guidelines". KDIGO held the first conference in Amsterdam in November 2004. The recommendations from the conference were ratified by the KDIGO board of directors in Paris in December 2004 offering, as a position statement, a clearer definition of CKD and its classification (Tables 1.1. and 1.2.) and practical advice on its screening and management.

Table 1.1. *Criteria for the definition of chronic kidney disease (CKD)*

Kidney damage for ≥ 3 months, as defined by structural or functional abnormalities of the kidney, with or without decreased GFR, that can lead to decreased GFR, manifest by either:
• Pathologic abnormalities; or • Markers of kidney damage, including abnormalities in the composition of the blood or urine, or abnormalities in imaging tests
GFR < 60 mL/min/1.73 m^2 for ≥ 3 months, with or without kidney damage

Table 1.2. *Definition and classification of chronic kidney disease. Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int 2005;67:2089.*

		Classification by severity		
Stage	Description	GFR ml/min/1.73m^2	Related terms	Classification by treatment
1.	Kidney damage with normal or ↑ GFR	≥ 90	albuminuria, proteinuria, hematuria	T if kidney transplant, recipient
2.	Kidney damage with mild ↓ GFR	60 – 89	albuminuria, proteinuria, hematuria	
3.	Moderate ↓ GFR	30 – 59	chronic renal insufficiency, early renal insufficiency	
4.	Severe ↓ GFR	15 – 29	chronic renal insufficiency, late renal insufficiency, pre-ESRD	
5.	Kidney failure	< 15 (or dialysis)	renal failure, ureamia, end-stage, renal disease	
				D if dialysis (hemodialysis, peritoneal dialysis)

Treatment by dialysis or transplantation was added in this K/DOQI modified classification. According to Levey, this was deemed necessary to link with clinical care and policy, especially regarding reimbursement. The „T“ was added for all kidney transplant recipient at any level of GFR (CKD stages 1-5) and „D“ for dialysis for CKD stage 5. Irrespective of the level of GFR at which the dialysis was initiated, all patients treated with dialysis were designated as CKD stage 5D. To improve the classification the need for elucidation of the cause of CKD as well as the prognosis was expressed.

In line with these considerations, a growing body of literature is questioning the appropriateness of grouping all patients with similar GFR in the same CKD stage, given the considerable heterogeneity in the CKD population. Studies by Menon, O' Hare and their coworkers have shown that outcomes in the same CKD stage can

vary considerably depending on age, background cardiovascular risk, etiology and the rate of CKD progression. There are claims that staging system needs to be modified to reflect the severity and complications of CKD in order to allow identification and treatment of clinically relevant disease and avoidance of what seem exaggerated prevalence estimates. These considerations will probably be taken into account by the next K/DOQI Clinical Practice Guidelines for CKD.

1.2 Pathophysiology of kidney disease

When discussing the pathophysiology of CKD, renal structural and physiological characteristics, as well as the principles of renal tissue injury and repair should be taken into consideration.

Firstly, the rate of renal blood flow of approximately 400 ml/100g of tissue per minute is much greater than that observed in other well perfused vascular beds such as heart, liver and brain. As a consequence, renal tissue might be exposed to a significant quantity of any potentially harmful circulating agents or substances. Secondly, glomerular filtration is dependent on rather high intra- and transglomerular pressure (even under physiologic conditions), rendering the glomerular capillaries vulnerable to hemodynamic injury, in contrast to other capillary beds. In line with this, Brenner and coworkers identified glomerular hypertension and hyperfiltration as major contributors to the progression of chronic renal disease. Thirdly, glomerular filtration membrane has negatively charged molecules which serve as a barrier retarding anionic macromolecules. With disruption in this electrostatic barrier, as is the case in many forms of glomerular injury, plasma protein gains access to the glomerular filtrate. Fourthly, the sequential organization of nephron's microvasculature (glomerular convolute and the peritubular capillary network) and the downstream position of the tubuli with respect to glomeruli, not only maintains the glomerulo-tubular balance but also facilitates the spreading of glomerular injury to tubulointerstitial compartment in disease, exposing tubular epithelial cells to abnormal ultrafiltrate. As peritubular vasculature underlies glomerular circulation, some mediators of glomerular inflammatory reaction may overflow into the peritubular circulation contributing to the interstitial inflammatory reaction frequently recorded in glomerular disease. Moreover, any decrease in preglomerular or glomerular perfusion leads to decrease in peritubular blood flow, which, depending on the degree of hypoxia, entails tubulointerstitial injury and tissue remodeling. Thus, the concept of the nephron as a functional unit applies not only to renal physiology, but also to the pathophysiology of renal diseases. In the fifth place, the glomerulus itself should also be regarded as a functional unit with each of its individual constituents, i.e. endothothelial, mesangial, visceral and parietal epithelial cells - podocytes, and their extracellular matrix representing an integral part of the normal function. Damage to one will in part affect the other through different mechanisms, direct cell-cell connections (e.g., gap junctions), soluble mediators such as chemokines, cytokines, growth factors, and changes in matrix and basement membrane composition.

The main causes of renal injury are based on immunologic reactions (initiated by immune complexes or immune cells), tissue hypoxia and ischaemia, exogenic agents like drugs, endogenous substances like glucose or paraproteins and others, and

genetic defects. Irrespective of the underlying cause glomerulosclerosis and tubulointerstitial fibrosis are common to CKD.

An overview of the pathophysiology of CKD should give special consideration to mechanisms of glomerular, tubular and vascular injury.

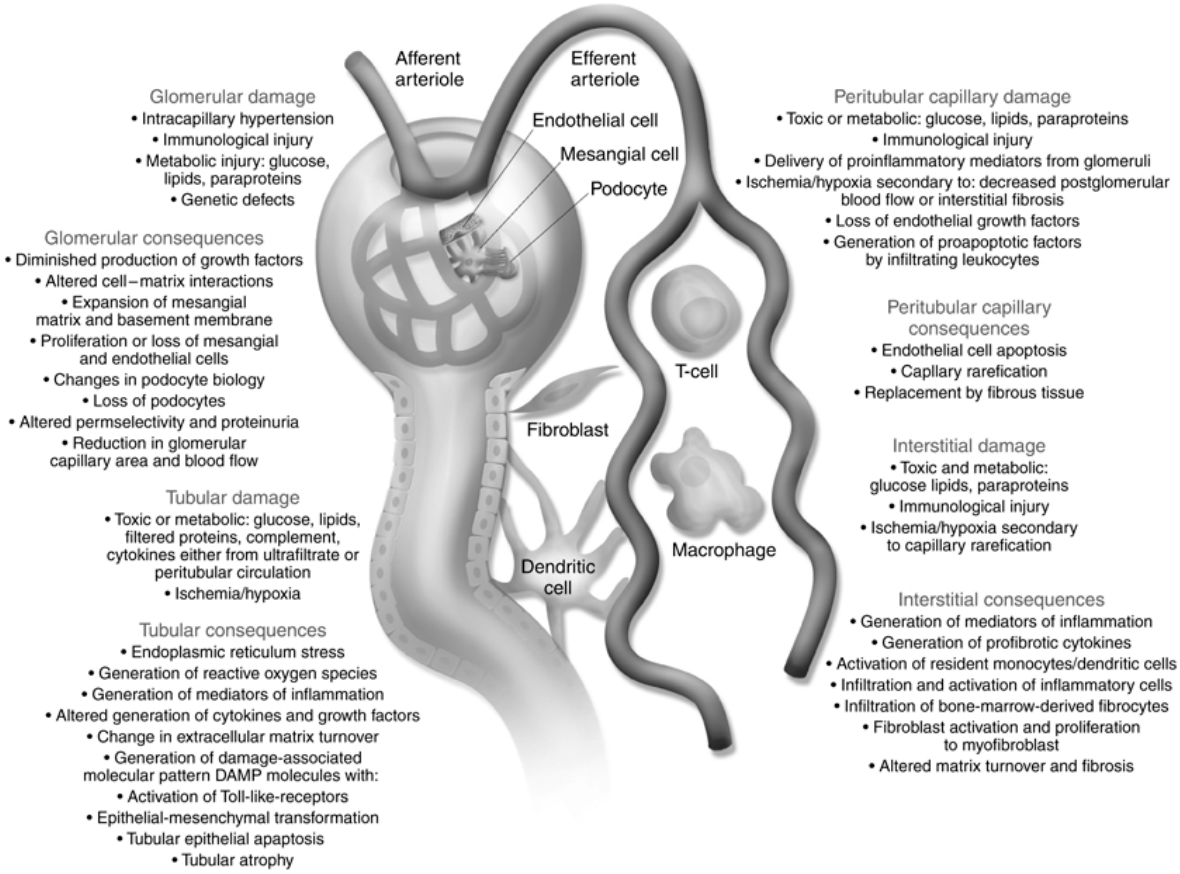

Figure 1.1. *Schlondorff DO. Overall scheme of factors and pathways contributing to the progression of renal disease. Kidney Int 2008;74:860-6.*

1.2.1 Mechanism of glomerular impairment

Hereditary defects account for a minority of glomerular disease. A prototype of an inherited glomerular disease is the Alport's syndrome or hereditary nephritis, usually transmitted as an X-linked dominant trait although autosomal dominant and recessive forms have been reported as well. In its classical X-linked form there is a mutation in the COL4A5 gene that encodes the α5 chain of type IV collagen located on the X chromosome. As a consequence, GBM is irregular with longitudinal layering, splitting or thickening, and the patient develops progressive glomerulosclerosis and renal failure. Other types of inherited glomerular disease are thin membrane syndrome, nail-patella syndrome, partial lipodystrophy, and familial lecithin-cholesterol acyltranferase deficiency.

Most **acquired glomerular disease** is triggered by immune mediated injury, metabolic and mechanical stress. From a pathological and pathogenetic point of view glomerular diseases can broadly be divided into three groups:

- nonproliferative (without cell proliferation) glomerular diseases without glomerular inflammation and without deposition of immunoglobulins (minimal change disease, idiopathic focal, and segmental glomerulosclerosis [FSGS]) or with deposition of immunoglobulins, but without glomerular inflammation, most likely because of subepithelial localization of immunoglobulins (e.g., membranous nephropathy)

- proliferative glomerular diseases with deposition of immunoglobulins leading to increased cellularity (proliferative glomerulonephrites, e.g., lupus nephritis, IgA nephropathy, anti-GBM, postinfectious GN), or with severe glomerular injury and inflammation, but without deposition of immunoglobulins (e.g., pauci-immune glomerulonephritis).

- heterogenous group of glomerular diseases in systemic diseases like glomerular disease in diabetes, amyloidosis and paraproteinemia.

The podocyte seems to occupy the central role in the pathogenesis of the first group of glomerular diseases as well as in diabetic nephropathy. This topic will be elaborated separately.

In the second group of glomerular diseases with cell proliferation, either deposition of immune complexes from the circulation or formed in situ lead to activation of intrinsic renal cells (via Fc receptors and complement cascade activation), resulting in inflammatory cell recruitment. Futhermore, severe glomerular injury and inflammation can occur without discernible immune complexes in the glomeruli, as in ANCA (antineutrophil cytoplasmic antibodies) positive glomerulonephritis. The offending etiologic agents are mainly unknown, with the rare exception of ß hemolytic streptococci in poststreptococcal glomerulonephritis, and hepatitis C virus in type 1 cryoglobulinemic membranoproliferative glomerulonephritis. Most antibody-mediated glomerulonephrites are initiated by the reactivity of circulatory antibodies and glomerular antigens, whereby antigens might be the components of normal glomerular parenchyma as in anti-GBM antibody disease (Goodpasture' syndrome), or the antigens are planted from the circulation within the glomeruli as in poststreptococcal glomerulonephritis (the in situ formation of immune complexes). The immune complexes formed in systemic circulation can be deposited and trapped in glomeruli (in cryoglobulinemic glomerulonephritis). Additional mechanism of antibody-mediated glomerular injury, but without immune complexes in the glomeruli, is represented by circulating autoantibody against neutrophil cytoplasmatic antigens (ANCA). Reactive oxygen species, protease, cytokines, chemokines and other inflammatory mediators originating from recruited and resident inflammatory cells play the key pathogenic roles.

Immune complexes can be deposited in the mesangium (as in IgA nephropathy, Henoch Schonlein purpura, lupus nephritis class II, postinfectious GN), in subendothelial (lupus nephritis class III, membranoproliferative GN), or subepithelial area (idiopatic membranous nephropathy or class V lupus nephritis, postinfectious GN), or along GBM (as in anti-GBM disease). The site of antibody deposition defines

the response to injury and clinicopathological presentation. A strong inflammatory reaction occurs only when circulating inflammatory cells can be activated by contact with immunoglobulins or soluble products released by intrinsic renal cells. Thereby, the deposition of antibodies in the subendothelial area, mesangium or membrane elicits a nephritic response, as the position of immune complexes enables activation of endothelial or mesangial cells which release soluble products and rapidly recruit leukocytes and platelets from the blood. Leukocyte-derived products, such as cytokines, lysosomal enzymes, reactive oxygen species, complement components and other, damage the vascular wall and filtration barrier and attract more leukocytes from the circulation. The subepithelial position of immune complexes (as in membranous nephropathy) leads to nephrotic response, as GBM precludes the contact between immune complexes and inflammatory cells from the circulation. Another reason for this kind of response is that large fluid flow from vascular lumen to Bowman's space does not permit inflammatory mediators formed in the subepithelium to diffuse retrogradely from epithelial to the endothelial layer and vascular lumen.

Tissue injury after IC deposition is mediated through complement activation resulting in the formation of C5-9 membrane attack complex which appears to be the major effector of glomerular injury through release of chemotactic C5a and C3a. C5-9-activated cells release chemokines and oxidant proteases, and upregulate adhesion molecules.

T-cells also act as mediators of glomerular injury and as modulators of the production of nephrite/ogenic antibodies, especially in pauci-immune GN. They interact through their surface receptor/CD3 complex with antigens presented in the clefts of MHC molecules of endothelial, mesangial and epithelial glomerular cells. This process is facilitated by the cell-cell adhesion and costimulatory molecules. Once activated, T-cells release cytokines and other mediators of inflammatory reaction, cytotoxicity and fibrogenesis. Soluble factors from T cells have been implicated in the pathogenesis of minimal change disease and focal and segmental glomerulosclerosis, but their identity has yet to be determined.

TGF-ß and connective tissue growth factor (CTGF) are important in glomerular fibrogenesis, as they stimulate glomerular cells to produce extracellular matrix (ECM), a key event in the progression of kidney disease, inhibiting the synthesis of tissue protease, mostly matrix metalloproteinase, which otherwise degradates matrix proteins.

Glomerular inflammation can either completely recover or resolve with a variable degree of fibrosis. The resolution process requires cessation of further antibodies production and immune complex formation, degradation and removal of deposited and circulating immune complexes, cessation of recruitment and clearing of inflammatory cells, dispersing of inflammatory mediators, normalization of endothelial adhesiveness, permeability and vascular tone, and clearance of proliferating resident glomerular cells.

Nonimmunologic glomerular injury. Hemodynamic, metabolic and toxic injuries can induce glomerular impairment alone or in conjunction with immunological processes.

Systemic hypertension translated to glomeruli and glomerular hypertension resulting from local changes in glomerular hemodynamics may cause glomerular injury. The kidney is normally protected from systemic hypertension by autoregulation which can be overwhelmed by high blood pressure, meaning that systemic hypertension is translated directly to glomerular filtration barrier causing glomerular injury. Chronic hypertension leads to arteriolar vasoconstriction and sclerosis with consequent secondary sclerosis and glomerular and tubulointerstitial atrophy. Different growth factors like angiotensin II, EGF, PDGF, and CSGF, TGF-ß cytokine, activation of stretch-activated ion channels and early response gene are involved in coupling high blood pressure to myointimal proliferation and vessel wall sclerosis.

Glomerular hypertension is normally an adaptive mechanism in remaining nephrons to increased workload resulting from nephron loss, whatever the cause. This sustained intraglomerular hypertension increases mesangial matrix production and leads to glomerulosclerosis by ECM accumulation. The process is mediated by TGF-ß in the first place, with a contribution of angiotensin II, PDGF, CSGF and endothelins.

Systemic and glomerular hypertension are not necessarily associated, as glomerular hypertension may precede systemic hypertension in glomerular disease.

Metabolic injury as that occurring in diabetes is discussed separately.

1.2.2 Mechanism of tubulointerstitial impairment

Regardless of the etiology, chronic kidney disease is characterized by renal fibrosis - glomerulosclerosis and tubulointerstitial fibrosis. The impairment of the tubulointerstitium (tubulointerstitial fibrosis and tubular atrophy) is at least as important as that of the glomeruli (glomerulosclerosis). There is a common consensus that the severity of tubulointerstitial injury correlates closely (and better than glomerular injury) with long-term impairment of renal function. This is not surprising, considering that tubules and interstitium occupy more than 90% of the kidney volume. As very recently summarized by Fine and Norman, tubulointerstitial fibrosis encompasses a number of characteristic features including an inflammatory cell infiltrate which results from both activation of resident inflammatory cells and recruitment of circulating inflammatory cells; an increase in interstitial fibroblasts due to increased proliferation and decreased apoptosis of resident interstitial cells, as well as recruitment of cells to the tubulointerstitium; the appearance of myofibroblasts expressing the cytoskeletal protein α-smooth muscle actin, which arise by differentiation of resident interstitial fibroblasts and infiltrating cells and via transdifferentiation; accumulation of extracellular matrix (ECM) as the net result of increased synthesis of ECM components and decreased ECM degradation, mostly by specific metalloproteinases that are under the control of specific inhibitors; tubular atrophy as a consequence of apoptosis and epithelial–mesenchymal transdifferentiation (EMT); and rarefaction of peritubular capillaries. The development of fibrosis is associated with an increase in the expression of proinflammatory, vasoconstrictive and profibrotic factors.

Renal fibrogenesis. The initial insult leads to inflammatory response with the generation and local release of soluble mediators, an increase in local vascular permeability, activation of endothelial cells, extravasation of leukocytes along the endothelium, subsequent secretion of various mediators by infiltrating leukocytes and tubulointerstitial cells, and activation of profibrotic cells. As a consequence a vicious cycle of cell stress is initiated generating profibrotic and proinflammatory mediators, leukocyte infiltration and fibrosis.

Induction and development of the inflammatory response. Leukocytes migrate from the circulation through postcapillary venules and peritubular capillaries into the interstitium following gradients of chemoattractants and chemokines. All tubular cells can generate soluble mediators when stimulated by hypoxia, ischaemia, infectious agents, drugs, and endogenous toxins like lipids, high glucose, paraproteins or genetic factors as in cystic renal diseases. Glomerular disease is usually associated with a variable degree of tubulointerstitial injury and inflammation because tubular cells are exposed to proteins which are normally not filtered. The factors involved in the formation of tubulointerstitial inflammatory infiltrates are: proteinuria, immune deposits, chemokines, cytokines, calcium phosphate, metabolic acidosis, uric acid, lipids, hypoxia and reactive oxygen species.

The inflammatory infiltrate. Infiltrating inflammatory mononuclear cells are composed of monocytes/macrophages and lymphocytes, particularly T lymphocytes. CD4-positive T cells and CD3 T cells carrying chemokine receptors CCR5 and CxCR3 are closely associated with renal function. This inflammatory cells secrete profibrotic cytokines.

Profibrotic cytokines. Infiltrating inflammatory cells and resident interstitial macrophages release cytokines which stimulate fibroblasts to become myofibroblasts. The most important profibrotic factors involved in renal fibrogenesis are angiotensin II, TGF-ß1, CTGF, PDGF, FGF-2 (fibroblast growth factor -2), EGF, ET-1, tryptase mast cell. Angiotensin II induces TGF- ß synthesis in tubular epithelial cells and fibroblast. AII induces hypertrophy in tubular epithelial cells together with connective tissue growth factor (CTGF), independently of TGF- ß. It is currently assumed that TGF-ß1 is the key cytokine in renal fibrogenesis.

Fibroblast proliferation and activation. Fibroblasts proliferate and become active following infiltration of inflammatory cells into the tubulointerstitial space. To express α-smooth muscle actin, the fibroblasts must be activated by cytokines (mostly derived from infiltrating macrophages), change their phenotype and transit from fibroblasts to myofibroblasts. The important mitogens for renal fibroblast are PDGF, bFGF-2 and others, but no single profibrotic „master cytokine„ has been identified so far.

Epithelial-mesenchymal transition. Phenotypic conversion of epithelial cells into mesenchymal cells is known as the epithelial-mesenchymal transition. Evidence for EMT in human disease comes from utilization of mesenchymal marker proteins such as vimentin or S100A4, the human analogue of fibroblast-specific protein-1. The expression of these mesenchymal marker proteins in tubular epithelial cells was well correlated with renal function in IgA nephropathy, lupus nephritis and chronic allograft failure. TGF-ß1 is thought to be the most potent inducer of EMT, which may be induced by a variety of factors other than cytokines.

It has been shown lately that hypoxia-inducible factor-1 (HIF-1), considered to be master regulator of the adaptive response controlling expression of hundreds of genes, also stimulates EMT, which explains why hypoxia results in fibrosis and progressive renal failure. Hypoxia as a consequence of peritubular capillaries loss has been frequently observed in chronic kidney disease. It alters proximal tubular epithelial (PTE) matrix metabolism, promoting ECM accumulation, with a switch to production of interstitial collagen and suppression of matrix degradation. Exposure of PTE to hypoxia induces transition to myofibroblastic phenotype, whereas more prolonged exposure leads to mitochondrial injury and apoptosis consistent with the loss of tubular cells *in vivo*. In PTE, hypoxia also induces expression of fibrogenic factors. Reports from biopsies carried out in patients with diabetic nephropathy, IgA nephropathy, polycistic kidney disease, and chronic allograft nephropathy have confirmed increased expression of HIF, supporting the hypothesis that hypoxia is an important contributory factor in the pathogenesis of CKD in humans. Furthermore, changes in HIF expression correlate with the extent of tubulointerstitial injury.

Proteinuria and tubulointerstitial damage. Proteinuria can damage tubulointerstitium through multiple pathways including direct tubular toxicity, changes in tubular epithelial metabolism, induced cytokine and chemokine synthesis, and increased expression of adhesion molecules. (Abbate). Excess protein reabsorption in proximal tubule may exceed lysosomal processing capacity, lead to lysosomal rupture and result in direct tubular toxicity. There is a great variability in tubular toxicity induced by proteinuria. For example, patients with nephrotic range proteinuria exclusively consisting of albuminuria as in minimal change disease, rarely exhibit tubulointerstitial damage. Different experimental models have demonstrated generation of chemotactic factor for macrophages, secretion of chemokines such as monocyte chemoattractant protein-1 and RANTES, and expression of fractalkine (a chemokine promoting mononuclear cell adhesion). In addition to inducing chemokine secretion proteinuria may induce secretion of TGF-ß as well as that of adhesion intercellular adhesion molecule-1 and vascular adhesion molecule-1. In a study reporting on results from 119 renal biopsies the formation of interstitial infiltrates and the degree of tubulointerstitial fibrosis was associated with the level of expression of adhesion molecules.

The reversibility of renal fibrosis was demonstrated in different animal studies with relatively mild degrees of fibrosis. In this context BMP-7, which offers strategy to prevent the progression of renal disease and possibly even reverse fibrosis, has been extensively studied. However, only Fioretto has given evidence of reversibility of tubulointerstitial fibrosis in humans in a small group of patients with type 1 diabetes who underwent pancreas transplantation.

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