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Severity and Stages of Chronic Kidney Disease

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1. Introduction

Nearly ten years ago Nephrologists began using asystem of classification for chronic kidney disease (CKD). This was established in 2002 by the Kidney Disease Outcome Quality Initiative (KDOQI) to estimate kidney function in a given patient regardless of the etiology of the primary insult to the kidneys. Physicians were able place their patients in stages from mild disease to end stage renal disease (ESRD).CKD is defined as glomerular filtration rate (GFR) below 60 ml/min per 1.73 m^2 for 3 months or more.

Each stage served as a "mile marker" on life's road for the patient with CKD. The natural history of CKD usually is a steady decline in kidney function, as found in the relationship between the reciprocal of serum creatinine values and time. A percentage of patients do not follow this linear pattern, suggesting either worsening or improvement in their kidney function. Factors which may cause worsening of CKD in such individuals are often infections, dehydration, poor control of systemic blood pressure and exposure to nephrotoxins, in particular nonsteroidal anti-inflamatorydrugs and radiocontrast agents. Other individuals who do not follow the steady decline may actually show improvement in their GFR. The potential to improve the natural history of CKD is through tight blood pressure control and inhibition of rennin-angiotensin-aldosterone system.

2. Stages of chronic kidney disease

The early stages of kidney dysfunction are often clinically silent, especially when the condition is only slowly progressive and symptoms are nonspecific. Stages 1 & 2 show decreased kidney function without signs or symptoms of disease although the estimated GFR is less than 120 ml/min per 1.73 m^2 but greater than 60 ml/min per 1.73 m^2. The rate of progression is influenced by a wide range of factors which may or may not have the potential of modification and varies among different individuals and with the underlying cause of nephropathy.When the patient enters Stage 3 he or she has lost approximately half their kidney function. It is less likely for the kidney disease to progress unless more than 50% of the nephron function is lost. For example, individuals with a solitary kidney after unilateral nephrectomy for living kidney donation usually do not progress to CKD.Increased risk of natural progression with less than 50% of nephron loss can occur in persons of African ancestry with hypertensive nephrosclerosis. In 2008, the U.K National Institute of Health and Clinical Excellence (NICE) sub divided the stage 3 into 3A and 3B with estimated GFRs of 45 to 59 ml/min per 1.73 m^2 and 44 to 30 ml/min per 1.73 m^2

respectively. The NICE CKD guideline also suggested adding the suffix *p* to the stages in proteinuric patients.It has generally been assumed that the majority of patients with CKD stages 3B to 5 eventually progress to ESRD. A Canadian study showed the natural history of CKD stages 3 and 4 to be variable and reflecting the patient's risk factor profile.Stage 4 may present with hyperkalemia or problems with salt and water retention. The kidneys are no longer able to adjust to abrupt changes in sodium, potassium and fluid intake (or loss). Prior to initiation of renal replacement therapy, the patient's appetite may decrease, accompanied by weight loss and a decrease in the serum albumin. In CKD clinics, with patients seen at frequent intervals, the goal is to initiate dialysis before the patient becomes malnourished.

Stage	Description	GFR (ml/min/1.73m²)
1	Kidney damage with normal or ↑ GFR	≥ 90
2	Kidney damage with mild ↓ GFR	60-89
3	Moderate ↓ GFR	3A 45 – 59 3B 30 - 44
4	Severe ↓ GFR	15-29
5	Kidney Failure	< 15 (or dialysis)
The suffix p to be added to the stage in patients with proteinuria > 0.5 g/24h		

Table 1. Stages of CKD.

Two commonly used formulas to calculate creatinine clearance are the Cockcroft-Gault formula and MDRD formula.

Cockcroft-Gault formula: $GFR = \frac{(140 - Age) \times Mass(Kgs) \times (0.85 \ \ if \ \ female)}{72 \times Serum\ Cr}$

Modification of diet in renal disease (MDRD) formula:

$$GFR = 186 \times SCr.^{-1.154} \times Age^{-0.203} \times (1.212 \ if \ black) \times (0.742 \ \ if \ \ female)$$

3. Risk factors

It is estimated that by 2030,more than 2,000,000 Americans will need dialysis or transplantation. Who are these patients? What risk factors do they have?

Low birth weight individuals with a decreased number of nephrons, the elderly population losing 1 ml/min/year after the age of 30 and Americans of African descent with hypertension, are several groups of individuals at risk.About one half of patients starting dialysis in America have diabetes mellitus, with hypertension the second largest group. Autoimmune disorders, infections, kidney stones, cystic kidneys and toxins/medications round out the list. Microalbuminuria may indicate systemic endothelial dysfunction and may be associated with a prothrombotic state. Insulin resistance is mediated in part by aldosterone; blocking the receptor attenuates cardiovascular and renal injury.

The risk factors can be classified as those that increase the risk of development of kidney disease and those that increase the risk of adverse outcomes associated with CKD. The

factors which increase the risk for CKD are further classified into susceptibility and initiation factors; whereas factors which effect adverse outcomes are classified as progression factors and end stage factors. The association between variables and disease may be due to chance, a non-causal relation or may signify a true risk factor.

3.1 Risk factors for development of CKD

1. Susceptibility Factors

A susceptibility factor is one that increases susceptibility to kidney damage following exposure to an initiation factor. An ideal study design to study these factors would be to identify a population of individuals who are free of kidney disease and are exposed to an initiation factor and follow them for a period of time.

2. Initiation Factor

An initiation factor is one that directly initiates kidney damage in an individual who is susceptible to kidney damage. An ideal study design for identification of initiation factors is a prospective cohort study. This would involve identification and follow up of a group of individuals free of kidney disease at baseline, with known susceptibility factors and with or without exposure to initiation factors, for the development of kidney disease.

3.2 Risk factors effecting adverse outcome of CKD

1. Progression Factors

Progression factors worsen the kidney damage caused by initiation factors and lead to further decline in kidney function. Indicators of progression may include progression of microalbuminuria to overt proteinuria or reduced GFR, rate of decrease of GFR, or development of kidney failure necessitating dialysis or transplantation.

2. End-Stage Factors

End –stage factors are those that exacerbate the morbidity and mortality associated with kidney failure. Examples of indicators of mobidity include hospitalizations, poor quality of life measures, and cardiovascular disease complications.

3.3 Risk factors for progression of chronic kidney disease

1. Proteinuria

   Proteinuria is associated with faster rates of CKD progression. It contributes to nephron loss; filtered proteins are reabsorbed by the proximal tubular cells. Tubular cell contents may leak into the interstitium. This can cause macrophage infiltration and inflammatory mediators produced by them. The MDRD study showed proteinuria to be the strongest predictor of kidney disease progression in non diabetic patients. The REIN study done in non diabetic patients with proteinuria, showed the protein excretion rate to be the best single predictor of GFR decline to ESRD. This finding was independent of the initial insult.

   The US Collaborative Study in type 1 diabetic patients with >500mg proteinuria/day and serum creatinine values of 2.5mg% or less showed a 50% reduction in the risk of combined endpoints (death, dialysis, transplantation) in patients treated with an ACE inhibitor.

Risk Factor	Definition	Examples
Susceptibility factors	Increase susceptibility to kidney damage	Older age, family history of chronic kidney disease, reduction in kidney mass, low birthweight, U.S. racial or ethnic minority status, low income or education
Initiation factors	Directly initiate kidney damage	Diabetes, high blood pressure, autoimmune diseases, systemic infections, urinary tract infections, urinary stones, lower urinary tract obstruction, drug toxicity
Progression factors	Cause worsening kidney damage and faster decline in kidney function after initiation of kidney damage	Higher level of proteinuria, higher blood pressure, poor glycemic control in diabetes, smoking
End-stage factors	Increase morbidity and mortality in kidney failure	Lower dialysis dose (Kt/V), temporary vascular access, anemia, low serum albumin level, late referral

Table 2. Risk Factors for Chronic Kidney Disease and its Outcomes.

The IDNT Study looked at type 2 diabetic patients treated with placebo, ibesartan or amlodipine. The ARB outperformed the placebo group and calcium channel patients in reaching doubling of the serum creatinine, ESRD, death by 20% and 23% respectively.

2. Hypertension
   Blood pressure should be lowered to <120/80.
   Patients with blood pressure 120-129/80-84 have a 1.6 fold greater risk of developing ESRD and those with pressure >210/120 have a 4.2 fold risk of ESRD.
   The MRFIT study showed that hypertension was an independent risk factor for the development of ESRD.
3. Smoking cessation- smoking is a risk factor in the progession to kidney failure
   Hallan, S & Orth, S. KI 2011.157
4. Glycemic control
   Blood pressure control is more important with progression of CKD in the diabetic patient, whereas hyperglycemia is important with the initiation of diabetic nephropathy.
5. Management of dyslipidemia
   LDL stimulates mesangial cell proliferation and the synthesis of proinflammatory molecules.
   No large study is available to show that control of lipids is effective in slowing the progression of CKD. The SHARP study showed that CKD patients receiving simvastatin and ezetimibe had approximately 15% fewer strokes and MIs.

4. Mechanism of progression

The characteristic structural change in CKD is scarring associated with glomerulosclerosis, tubulointerstitial fibrosis, and vascular sclerosis. After this initial insult the kidney goes down on one of the two paths, healing and functional recovery or scarring with loss of

kidney function progressing to CKD. It is less known what leads the kidney to which pathway.

Healing primarily occurs in Acute Kidney Injury (AKI) and acute interstitial nephritis, when treatment is instituted early in its course. Healing is also a hallmark of acute post infectious glomerulonephritis. Renal function typically recovers within few weeks of acute nephritic process.Chronic kidney damage on the other hand is usually induced by diabetes, hypertension, chronic glomerulonephritits, or chronic exposure to infections or nephrotoxins, progress to scarring with loss of function and CKD. (Fig. 1)

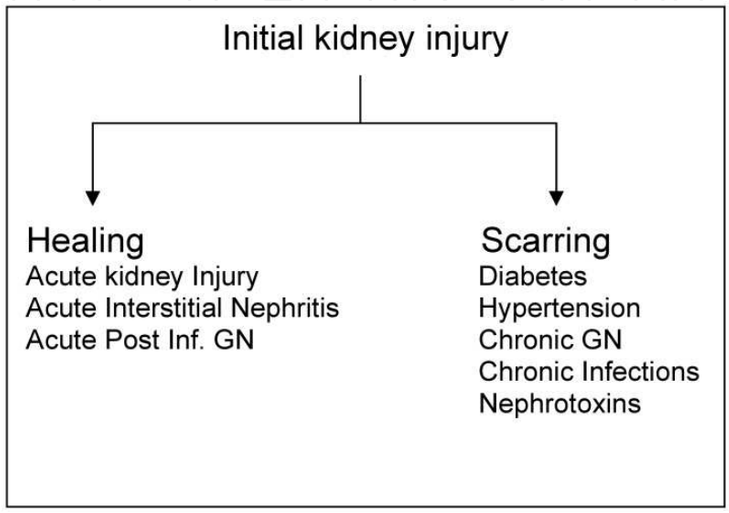

Fig. 1. Progression of initial kidney injury.

Renal cell injury results in loss of glomerular capillaries and cellular elements are replaced by extracellular matrix and fibrous tissue. Acute severe glomerulonephritis damages the capillaries and endothelium whereas sub-acute and chronic glomerulonephritis affect the mesangium or the podocytes. Progressive renal scarring is associated with progressive tubular cell loss and atrophy.

4.1 Role of intrinsic renal cells in kidney damage

Endothelium: Damage to the protective anticoagulant and anti-inflamatory endothelial capillary lining in acute glomerulonephritis, transforms it into a pro-inflammatory surface leading to accumulation of inflammatory cells and platelets within golmerular capillaries as well as the stimulation of mesangial proliferation. Glomerular endothelial damage can also be due to a metabolic insult as in diabetes or a physical hemodynamic stress as in hypertension.

Mesangium: Mesangial cells respond to injury either with death, transformation, proliferation and migration,or synthesis and deposition of extracellular matrix (ECM). Scarring is usually characterized by uncontrolled mesangial proliferation and excessive deposition of mesangial matrix. This process is driven by a number of growth factors like transforming growth factor β1 (TGFβ1), platelet derived growth factor (PDGF), and fibroblast growth factor (FGF).

Podocytes: After an injury to the podocytes, the glomerular basement membrane is exposed to the parietal epithelial cells leading to the formation of capsular adhesions and segmental glomerulosclerosis. This may lead to misdirected filtration with accumulation of amorphous material in the glomerular space. Misdirected filtration causes disruption of the glomerular-tubular junction resulting in atubularglomeruli. It may also contribute to tubular atrophy and interstitial fibrosis. Thus podocytes help in conserving the structural integrity of the glomerulus by forming a protective membrane over the basement membrane.

Tubular cells: As mentioned earlier, after the initial insult the tubular cells may undergo healing and recover renal function, but repeated insults stimulate epithelial mesenchymal transformation of tubular cells to myofibroblastic phenotype with excessive deposition of ECM. Thus tubular injury can lead to renal fibrogenesis.

Vascular cells: Vascular sclerosis is an intergral feature of renal scarring and is associated with progressive kidney failure in glomerulonephritis. Hyalinosis of afferent arterioles, in diabetes, and damage to the post-glomerular arteriole and peritubular capillaries cause interstitial ischemia and fibrosis.

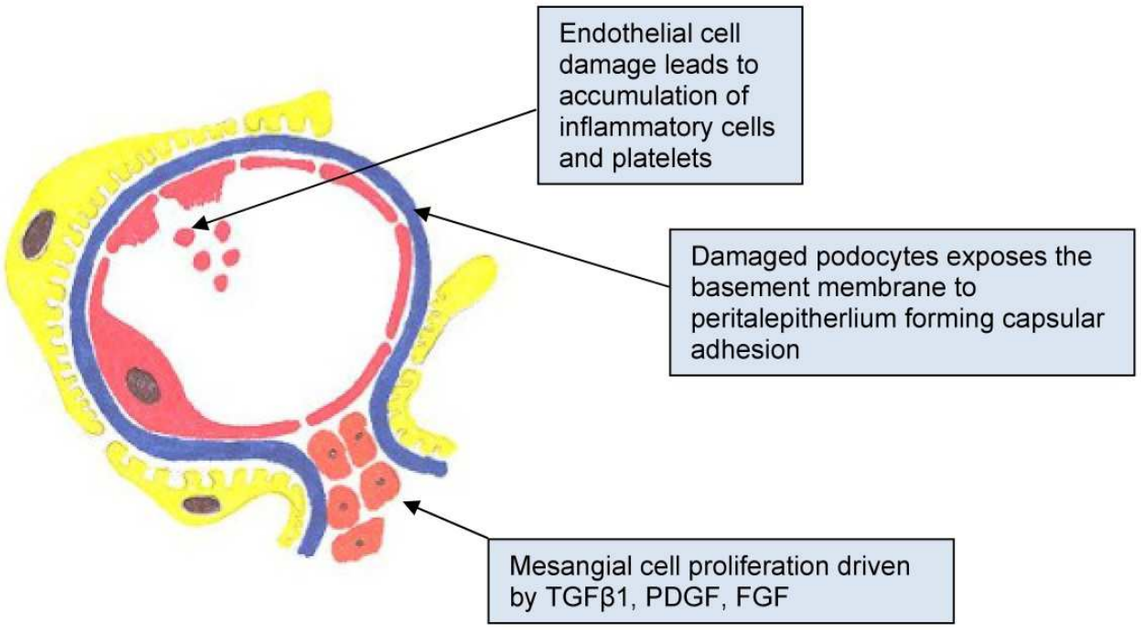

Fig. 2. Role of Intrinsic Cells in Kidney Damage.

4.2 Role of extrinsic cells in kidney damage

Infiltration of inflammatory cells into the glomeruli and the renal interstitium is the hallmark of glomerulosclerosis and tubuloiterstitial fibrosis.

Platelets and coagulation: Platelets and their release products within the damaged glomeruli stimulate a coagulation cascade which activate the mesangial cells to induce sclerosis. Thrombin stimulates glomerular TGF-β1 leading to production of mesangial ECM and inhibition of metalloproteinases.

Lymphocytes, Monocytes-Macrophages, Dendritic cells play important role in the formation of glomerulosclerosis by causing inflammation.

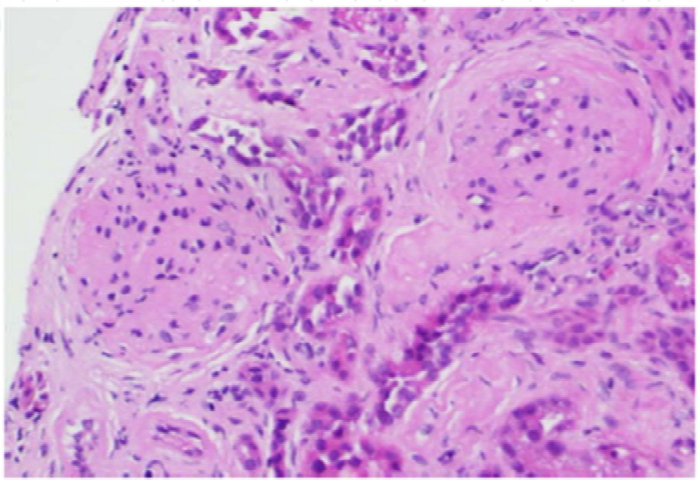

Fig. 3. Deposition on of ECM within and around the glomerulus.

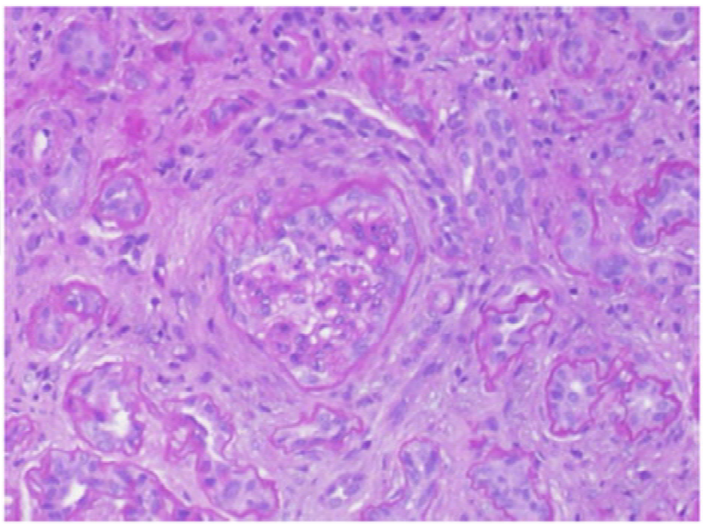

Fig. 4. Glomerular hypercellularity due to proliferation of intrinsic glomerular cells and intracapillary leukocytes.

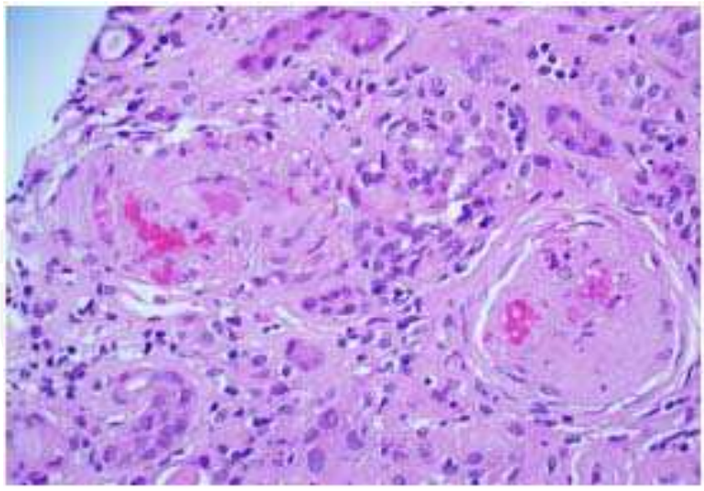

Fig. 5. Capillary tufts almost replaced by the fibous tissue forming glomerular scarring.

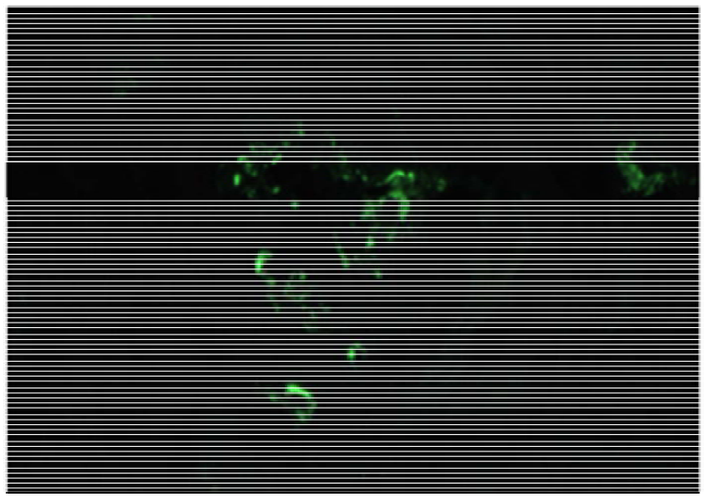

Fig. 6. Immunofluorescent stain shows deposition of coarsely granular deposits of complement C3.

4.3 Role of angiotensin II, hypertension and hyperfiltration

With progression of kidney disease the afferent arteriole tone decreases to a much larger extent than the efferent tone. As a result intra-glomerular pressure rises leading to hyperfiltration. Angiotensin II aides in hyperfiltration through its vasoconstrictor effect predominantly on the efferent arteriole. Apart from its hemodynamic effects, Angiotensin II acts directly on the glomerular membrane. It acts on the angiotensin II receptors on the surface of the podocytes, altering their permselective property, by contracting the foot processes. This allows proteins to escape in the urinary space.

Angiotensin II also induces proliferation ofglomerular cells and fibroblasts. It acts on AT1 receptors on tubular cells causing hypertrophy, which results in increased synthesis of collagen type IV. It increases macrophage activation and phagocytosis responsible for the inflammatory component associated with CKD.

4.4 Role of proteinuria

Proteinuria is not only a marker of kidney damage, but also contributes to nephron damage. Filtered proteins are reabsorbed from the proximal tubule. Damaged tubular basement membrane causes leakage of tubular content into the interstitium, thereby causing macrophage infiltration. Macrophages produce inflammatory mediators thus mounting an immense inflammatory reaction inside the renal interstitium.

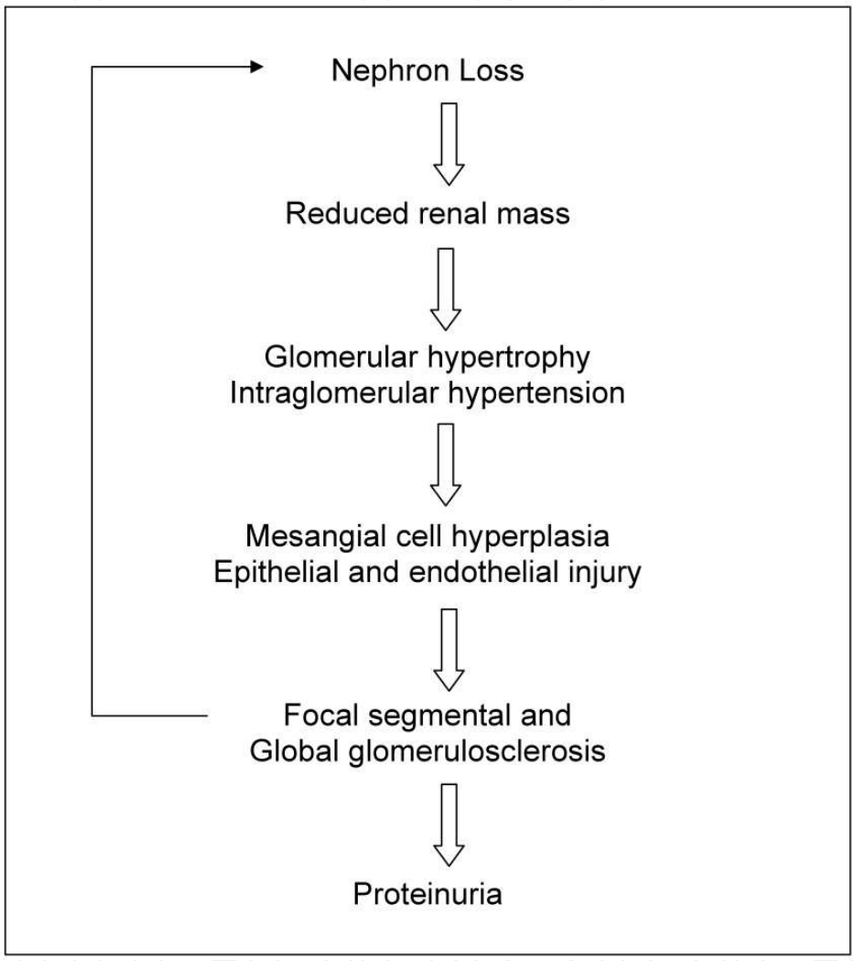

Fig. 7. Focal segmental and global Glomerulosclerosis and nephron loss is a vicious circle ultimately leading to proteinuria.

5. Pathology of CKD

Fibrosis in the kidneys initiated by a variety of insults may not be a uniform process.

Progressive disease in diabetic patients may be related to endothelial nitric oxide deficiency with resultant endothelial dysfunction.The eventual pathology of the above mentioned series of events lead to two major histologic characteristic of CKD, focal segmental glomerulosclerosis and tubulointerstitial fibrosis. An initial insult to the kidneys will cause nephron loss.The remaining nephrons work harder to compensate for the lost nephrons

(compensatory hypertrophy). This leads to hemodynamic changes including glomerular hypertension and hyperfiltration. There is reduced afferent arteriolar resistance and intraglomerular pressure rises with increased filtration by the remaining nephrons. The intrinsic and extrinsic cells contribute to sclerosis as mentioned above contributing to the focal and segmental glomerulosclerosis.

Tubulointerstitial injury results from ischemia of tubule segments downstream from sclerotic glomeruli. Acute and chronic inflammation in the adjacent interstitium, and damage of pericapillary blood supply also contribute to tubular injury. The above events along with proteinuria eventually lead to tubulointerstitial fibrosis.

Angiotensin II increases vascular tone (predominantly post-glomerular) and affects intraglomerular pressure. The increased pressure alters the structure of the pores in the glomerular basement membrane (GBM) and increases proteinuria.

5.1 Clinical manifestation and management

What is the best way to manage these individuals? In the outpatient setting, achecklist for each patient ensures that each individual's needs are met. A list of "ten commandments" for the CKD patient is:

1. Estimate the GFR and stage the patient's CKD.
2. Round up the usual suspects. Diabetes and hypertension account for almost ¾ of the patient population. Urinalysis, serologies, sonography and biopsy (if necessary) to make the diagnosis.
3. Fix what you can. Discontinue NSAIDs, correct volume depletion and treat BPH (men) and bladder dysfunction (women).
4. Treat hypertension. Goal of therapy is <130/80.
   Use ACE, ARB, both, renin blockers, calcium channel blockers, aldosterone antagonists, loop diuretics as needed.
5. Measure (spot urine protein /creatinine) and treat proteinuria. The goal is<300mg/day. Maximize the dose of an ACE inhibitor, then add an ARB at ½ full dose and increase to reach goal. Loop diuretics are essential to manage edema fluid and offset the development of hyperkalemia. Renin blockers and aldosterone antagonists are added with monitoring of the patient's potassium and creatinine. If the potassium rises to greater than 5.5 meq/l or if the serum creatinine increases more than 30% above baseline, dosages will need to be decreased.
6. Treat anemia of CKD with an ESA if there is no blood loss and iron stores are adequate. Check thyroid function, B-12, folic acid levels. The target Hgb is >10g/dl. Parenteral iron may be needed to keep the TSAT > 25%.
7. Give base supplements to correct metabolic acidosis. Untreated acidosis causes osteopenia and muscle catabolism, along with the release of calcium and phosphorous from bone. Sodium bicarbonate is replaced at 0.5-1.0 meq/kg/day.
   Treat hyperurricemia with allopurinol if the eGFR is >30 ml/min.
8. Phosphate binders, precursor vitamin D and active D (when necessary). We are using both calcium and non-calcium containing binders in our clinic. We try to keep serum calcium levels less than or equal to 9.5 mg%. Vitamin D2 and 3 are used in patients with 25(OH)D levels less than 30 ng/ml. Active vitamin D is used to control elevated iPTH levels and the effects of secondary HPT.

9. Have a nutritionist help patients maintain caloric intake. Protein restriction is difficult and may lead to malnutrition in patients with already poor appetites. We encourage protein supplementation in our CKD patients. The phosphorus level will increase, however, we try to maintain the patient's albumin predialysis or pretransplantation. Patients are started on a 2 gram potassium diet and educated about avoidance of foods high in potassium. Loop diuretics + base supplements aid in the management of hyperkalemia. Resin exchange binders are reserved for values greater than 6 as they cause diarrhea, bicarbonate loss and may worsen acidemia and further increase the serum potassium value.
10. Education and preparation for hemodialysis or peritoneal dialysis. See if acandidate is available for transplantation. We encourage patients to have a fistula constructed after they have attended the education class and decide to do in center or home hemodialysis. These are patients generally in late stage 3 CKD.

Diabetic patients should maintain euglycemia, insulin requirements may decrease as CKD progresses. Metformin should be avoided and glipizide isthe preferred oral agentbecause it is not downgraded to a metabolite excreted by the kidneys.

6. Summary

CKD will remain a health concern into the future. CKD clinics managing patients in a coordinated fashion with nutritionists and surgeons will improve lives. Better blood pressure control with diminution of proteinuria will slow the progress of established disease. Attention to acidemia and hyperruricemia will also be beneficial. New insights into the pathogenesis and treatment of diabetes may help manage the number one cause of kidney failure in America.

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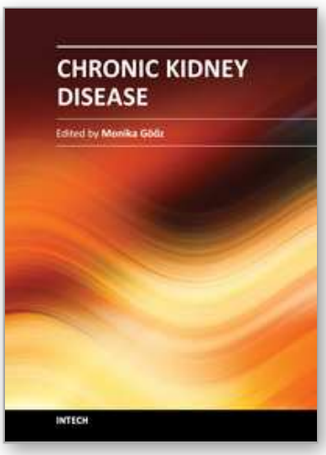

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Chronic kidney disease is an increasing health and economical problem in our world. Obesity and diabetes mellitus, the two most common cause of CKD, are becoming epidemic in our societies. Education on healthy lifestyle and diet is becoming more and more important for reducing the number of type 2 diabetics and patients with hypertension. Education of our patients is also crucial for successful maintenance therapy. There are, however, certain other factors leading to CKD, for instance the genetic predisposition in the case of polycystic kidney disease or type 1 diabetes, where education alone is not enough.

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