Section A-Research paper

An Overview about Chronic kidney disease

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Abstract

Chronic kidney disease (CKD) is a clinical syndrome secondary to the definitive change in function and/or structure of the kidney and is characterized by its irreversibility and slow and progressive evolution. Another important aspect is the pathology rep-resents a higher risk of complications and mortality, especially cardiovascular-related. An adult patient is identified with CKD when they present, for a period equal to or greater than three months, glomerular filtration rate (GFR) lower than 60 ml/min/1.73 m2, or GFR greater than 60 ml/min/1.73 m2, but with evidence of injury of the renal structure. Some indicators of renal injury are albuminuria, changes in renal imaging, hematuria/leukocyturia, persistent hydroelectrolytic disorders, histological changes in kidney biopsy, and previous kidney transplantation. Albuminuria is defined by the presence of more than 30 mg of albumin in the 24-hour urine or more than 30 mg/g of albumin in an isolated urine sample adjusted by urinary creatinine. The main causes of CKD include diabetes, hypertension, chronic glomerulonephritis, chronic pyelonephritis, chronic use of anti-inflammatory medication, autoimmune diseases, polycystic kidney disease, Alport disease, congenital malformations, and prolonged acute renal disease.

Keywords: Chronic kidney disease

Introduction

Chronic kidney disease (CKD) is a clinical syndrome secondary to the definitive change in function and/or structure of the kidney and is characterized by its irreversibility and slow and progressive evolution. Another important aspect is the pathology rep-resents a higher risk of complications and mortality, especially cardiovascular-related**(1).**

An adult patient is identified with CKD when they present, for a period equal to or greater than three months, glomerular filtration rate (GFR) lower than 60 ml/min/1.73 m2, or GFR greater than 60 ml/min/1.73 m2, but with evidence of injury of the renal structure. Some indicators of renal injury are albuminuria, changes in renal imaging, hematuria/leukocyturia, persistent hydroelectrolytic disorders, histological changes in kidney biopsy, and previous kidney transplantation **(2).**

Albuminuria is defined by the presence of more than 30 mg of albumin in the 24-hour urine or more than 30 mg/g of albumin in an isolated urine sample adjusted by urinary creatinine. The main causes of CKD include diabetes, hypertension, chronic glomerulonephritis, chronic pyelonephritis, chronic use of anti-inflammatory medication, autoimmune diseases, polycystic kidney disease, Alport disease, congenital malformations, and prolonged acute renal disease **(1).**

CLASSIFICATION

CKD is categorized into five stages, according to the GFR, and in three stages, according to the albuminuria, as shown in the tables below **(3):**

TABLE(1): CKD STAGE; GFR = GLOMERULAR FILTRATION RATE **(1).**

Stages	**GFR value ml/min/1.73m2**	**Classification**
I	>90	Normal or High
II	60-89	Slightly decreased
IIIA	45-59	Mild to moderately decreased
IIIB	30-44	Moderately to severely decreased
IV	15-29	Severely decreased
V	<15	Kidney failure

TABLE(2):CATEGORIES ALBUMINURIA; A/C RATIO = ALBUMIN/CREATININE RATIO IN ISOLATED URINE SAMPLES**(1).**

Category	**24-Hour Albuminuria mg/24h**	**A/C RatioMg/g**	**Classification**
A1	<30	<30	Normal to discrete
A2	30-300	30-300	Moderate
A3	>300	>300	Severe

Therefore, an adult patient with diabetic nephropathy, GFR estimated = 42 ml/min, and albuminuria of 200 mg/24 hours for over three months is classified as a CKD stage IIIB A2 patient **(4).**

It is worth remembering that albuminuria be-tween 30-300 mg/g used to be called ‘’microalbuminúria’’, and greater than 300 mg/g, “macroalbuminuria’’. The inclusion of the degree of albuminuria in the CKD classification is justified as a way of estimating the risk of progression of renal dysfunction, as shown in the table below**(1).:**

TABLE(3): RISK OF RENAL OUTCOMES ACCORDING TO THE GFR AND ALBUMINURIA; GFR: GLOMERULAR FILTRATION RATE IN ML/MIN/1.73 M2**(1).**

Albuminuria				
	GER	<30mg/g	30-300 mg/g	>300 mg/g
Stage 1	≥90	low risk	Moderate risk	High risk
Stage 2	60-89	low risk	Moderate risk	High risk
Stage 3A	45-59	Moderate risk	High risk	Very High risk
Stage 3B	30-44	High risk	Very High risk	Very High risk
Stage 4	15-29	Very High risk	Very High risk	Very High risk
Stage 5	<15	Very High risk	Very High risk	Very High risk

The staging system shown above helps physicians determine the method and intensity of monitoring that will be applied to CKD patients. A more accurate risk prediction for individual patients can be achieved by the development of risk prediction tools. In addition to the GFR and albuminuria, the cause of the kidney disease, as well as other factors (such as age, sex, race, cholesterol levels, smoking, and others), should also be considered in the prognosis estimate**(1).**

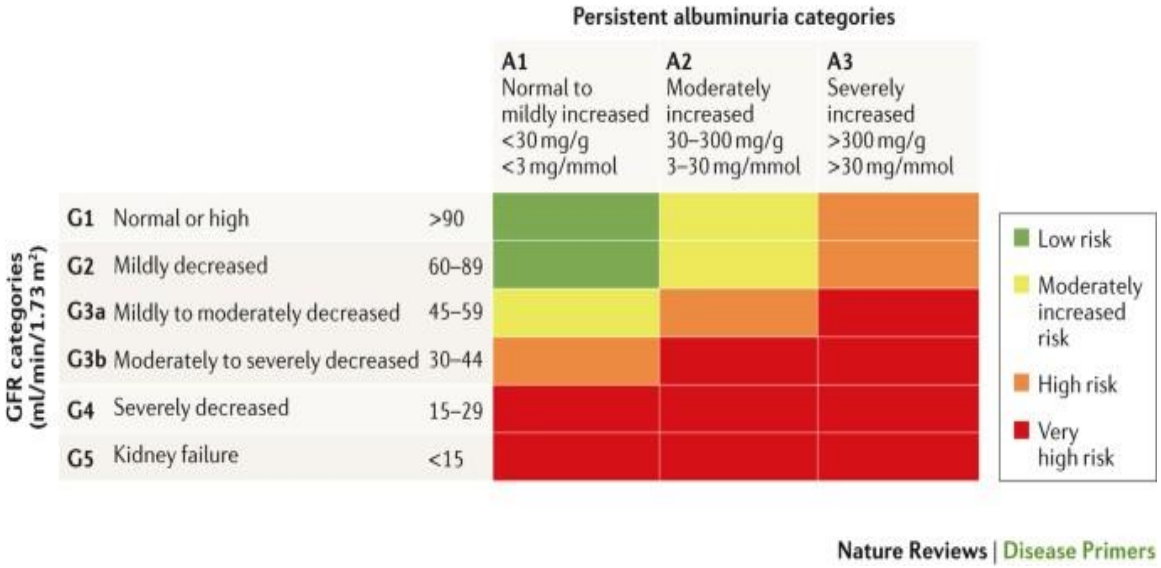

Figure 1: The KDIGO classification of CKD.

This Kidney Disease Improving Global Outcomes (KDIGO) 2D matrix incorporates the level of albuminuria (given as a ratio to creatinine (in mg per g) and divided into three categories) and the glomerular filtration rate (GFR) — that is, the level of kidney function — to describe the risk of patients with chronic kidney disease (CKD) progressing to adverse outcomes (such as progression to end-stage renal disease (ESRD), cardiovascular disease, hospitalization, acute kidney injury or death). Notably, in primary care settings, proteinuria is generally measured rather than measuring albuminuria specifically; however, the proteinuria dipstick results can be used to approximate the albuminuria stages. Additionally, GFR can either be estimated using various clinical equations or directly measured using dyes. The KDIGO matrix defines different stages of CKD referred as, for example, CKD G2A2 whereby the GFR is 60–89 ml/min/1.73 m^2 and albuminuria is moderately increased; such a patient would have a moderately increased risk of progressing to ESRD. However, the staging for CKD G2–G4 might underestimate the extent of irreversible nephron loss**(5).** For example, if total GFR relies on the filtration capacity of single nephrons ($GFR_{(single\text{-}nephron)}$) and the number of nephrons, $GFR_{(single\text{-}nephron)}$ has to increase to compensate for nephron loss to maintain total GFR. However, full compensation is no longer possible with ongoing nephron loss as occurs with physiological ageing **(6).** and total GFR declines owing to further reductions in nephron number. Additionally, serum creatinine underestimates nephron loss because it increases late in the disease process, when more nephrons are lost than would be implied by GFR alone. Finally, the prognostic value of the matrix suffers from being based on studies potentially having a false-positive rate of ~30–35% owing to a lack of repeat analysis after 3 months (that is, true CKD diagnoses were not consistently obtained) **(7).**

STAGING

The justification for staging asymptomatic individuals for CKD is that early detection may allow the implementation of therapeutic interventions and avoid the inappropriate exposure to nephrotoxic agents, which can slow the CKD progression to the terminal stage. Another important aspect is that the detection of CKD also identifies an important risk factor for cardiovascular disease. An additional ad-vantage of an early diagnosis is to facilitate the adjustment of medication dose and allow better preparation for renal replacement therapy if indicated **(8).**

The presence of the following risk factors determines the screening for CKD in adults (9):

• History of diabetes, hypertension, cardiovascular disease (CVD), human immunodeficiency virus (HIV) or hepatitis C virus infection, malignancy, autoimmune diseases, nephrolithiasis, or recur-rent urinary tract infections.

• Family history of renal disease.

Patients selected for CKD assessment should undergo (1):

• Measurement of serum creatinine and GFR estimate by mathematical formulae;

• Determination of albuminuria, for which the preferred method is the measurement of the albumin/creatinine ratio in the urine of an isolated urine sample due to its ease and good correlation with the excretion in the 24-hour urine **(10);**

• Imaging exam, particularly an ultrasound of the kidney and urinary tract.

Some practical aspects of detecting CKD should be remembered(4):

• The detection of CKD based on the estimated GFR is a more accurate assessment of renal function than the serum creatinine alone.

• Recent studies show that the EPI-CKD (Chronic Kidney Disease Epidemiology Collaboration) formula provides a more accurate prediction of prognosis of renal outcomes and presents less bias that the MDRD (Chronic Kidney Disease Epidemiology Collaboration equation) formula.

• The albumin/creatinine ratio in the urine of an isolated sample is a more sensitive and specific marker of CKD than the protein/creatinine ratio.

EPIDEMIOLOGY

CKD is very prevalent in the general adult population. Data from the United States estimate a prevalence of 13.1% among adults, which has increased over time **(11).** In Brasil , estimates of the prevalence of the disease are uncertain. A recent study reviewed the data available in the literature and found that the prevalence varied according to the method employed in the definition of the disease; by populational criteria, 3-6 million individuals are estimated to have CKD **(12).** The 2017 census by the Brazilian Society of Nephrology (BSN) reported that the total estimated number of patients on dialysis was 126,583, and the national estimates of the prevalence rates and incidence of patients under dialysis treatment per mil-lion population (pmp) was 610 **(13).**

In addition to being highly prevalent, CKD is associated with a higher risk of cardiovascular disease, severity, and death. In fact, global data from 2013 showed that the reduction in GFR was associated with 4% of deaths worldwide, i.e., 2.2 million deaths. More than half of those deaths were due to cardio-vascular causes, while 0.96 million were related to end-stage renal disease11. The aforementioned SBN census found a gross annual mortality rate of 19.9% on dialysis **(1).**

ETIOLOGY

The causes of CKD vary globally, and the most common primary diseases causing CKD and ultimately end-stage renal disease (ESRD) are as follows **(14):**

- Diabetes mellitus type 2 (30% to 50%)
- Diabetes mellitus type 1 (3.9%)
- Hypertension (27.2%)
- Primary glomerulonephritis (8.2%)
- Chronic Tubulointerstitial nephritis (3.6%)
- Hereditary or cystic diseases (3.1%)
- Secondary glomerulonephritis or vasculitis (2.1%)
- Plasma cell dyscrasias or neoplasm (2.1)
- Sickle Cell Nephropathy (SCN) which accounts for less than 1% of ESRD patients in the United States**(15).**

CKD may result from disease processes in any of the three categories: prerenal (decreased renal perfusion pressure), intrinsic renal (pathology of the vessels, glomeruli, or tubules-interstitium), or postrenal (obstructive) **(15).**

Prerenal Disease

Chronic prerenal disease occurs in patients with chronic heart failure or cirrhosis with persistently decreased renal perfusion, which increases the propensity for multiple episodes of an intrinsic kidney injury, such as acute tubular necrosis (ATN). This leads to progressive loss of renal function over time**(15).**

Intrinsic Renal Vascular Disease

The most common chronic renal vascular disease is nephrosclerosis, which causes chronic damage to blood vessels, glomeruli, and tubulointerstitium **(15).**

The other renal vascular diseases are renal artery stenosis from atherosclerosis or fibro-muscular dysplasia which over months or years, cause ischemic nephropathy, characterized by glomerulosclerosis and tubulointerstitial fibrosis**(16).**

Intrinsic Glomerular Disease (Nephritic or Nephrotic)

A nephritic pattern is suggested by abnormal urine microscopy with red blood cell (RBC) casts and dysmorphic red cells, occasionally white blood cells (WBCs), and a variable degree of proteinuria**.** The most common causes are post-streptococcal GN, infective endocarditis, shunt nephritis, IgA nephropathy, lupus nephritis, Goodpasture syndrome, and vasculitis **(17).**

A nephrotic pattern is associated with proteinuria, usually in the nephrotic range (greater than 3.5 gm per 24 hours), and an inactive urine microscopic analysis with few cells or casts. It is commonly caused by minimal change disease, focal segmental glomerulosclerosis, membranous GN, membranoproliferative GN (Type 1 and 2 and associated with cryoglobulinemia), diabetic nephropathy, and amyloidosis**(15).**

Some patients may be assigned to one of these two categories.

Intrinsic Tubular and Interstitial Disease

The most common chronic tubulointerstitial disease is polycystic kidney disease (PKD). Other etiologies include nephrocalcinosis (most often due to hypercalcemia and hypercalciuria), sarcoidosis, Sjogren syndrome, reflux nephropathy in children and young adults, There is increased recognition of the relatively high prevalence of CKD of unknown cause among agricultural workers from Central America and parts of Southeast Asia called Mesoamerican nephropathy **(18).**

Postrenal (Obstructive Nephropathy)

Chronic obstruction may be due to prostatic disease, nephrolithiasis or abdominal/pelvic tumor with mass effect on ureter(s) are the common causes. Retroperitoneal fibrosis is a rare cause of chronic ureteral obstruction**(15).**

RISK FACTORS FOR PROGRESSION OF CKD

Non-Modifiable CKD Risk Factors

Older age, male gender, a non-Caucasian ethnicity which includes African Americans, Afro-Caribbean individuals, Hispanics, and Asians (South Asians and Pacific Asians) all adversely affect CKD progression. Genetic factors which affect CKD progression have been found in different kidney diseases. In a population-based cohort study by Luttropp et al., single nucleotide polymorphisms in the genes *TCF7L2* and *MTHFS* were associated with diabetic nephropathy and CKD progression. In the same study, polymorphisms of genes coding for mediators of renal scarring and renin-angiotensin-aldosterone system (RAAS) were found to influence CKD progression **(19).**

Modifiable CKD Risk Factors

These include systemic hypertension, proteinuria, and metabolic factors. Systemic hypertension is one of the main causes of ESRD worldwide and the second leading cause in the United States after diabetes. The transmission of systemic hypertension into glomerular capillary beds and the resulting glomerular hypertension is believed to contribute to the progression of glomerulosclerosis. Night-time and 24-hour blood pressure measurement (ABPM) appear to correlate best with the progression of CKD. Systolic rather than diastolic BP seems to be predictive of CKD progression and has also been associated with complications in CKD **(20).**

Multiple studies in patients with diabetic and nondiabetic kidney diseases have shown that marked proteinuria (albuminuria A3) is associated with a faster rate of CKD progression. Also, a reduction in marked proteinuria by RAS blockade or by diet is associated with a better renal outcome. However, in large

intervention studies like Avoiding Cardiovascular Events Through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) and Ongoing Telmisartan Alone and in Combination with Ramipril Global End Point Trial (ONTARGET), significant declines in GFR were noted despite a marked reduction in albuminuria. Therefore, moderate level albuminuria (A2) is not a reliable surrogate marker for CKD progression, and reduction in albuminuria can be associated with both improving and worsening of CKD progression **(21).**

Multiple studies have linked the RAAS system in the pathogenesis of hypertension, proteinuria, and renal fibrosis throughout CKD. Subsequently, interventions targeting RAAS have proved effective in slowing the progression of CKD. This has led to the widespread use of RAAS blockers in proteinuric and diabetic kidney disease **(15).**

Obesity and smoking have been related to the development and progression of CKD. Also, metabolic factors such as insulin resistance, dyslipidemia, and hyperuricemia have been implicated in the development and progression of CKD **(22).**

DIAGNOSIS

The clinical presentation of CKD depends on the underlying disorder and the severity of renal impairment. Patients with early stages of CKD (G1–G2) are usually asymptomatic, but from CKD G3 onwards, patients may experience weakness related to anaemia and polyuria **(23).**

Detection and diagnosis

CKD can be detected during a routine periodic health assessment, during evaluation of individuals at risk of CKD , as a consequence of the incidental finding of abnormal laboratory values in connection with another acute or chronic illness, during an investigation of symptoms and/or signs relating to the kidneys or urinary tract (such as haematuria) or after discovery of abnormal laboratory values in a population-based screening programme. Importantly, the two biochemical parameters GFR and albuminuria used in the KDIGO matrix define and classify a 'generic' form of CKD; adding an aetiological diagnosis is both highly desirable and recommended by KDIGO (the so-called cause/GFR/albuminuria (CGA) classification system) whenever possible, such that the underlying conditions can be treated first to halt progression of CKD. Several tests can be performed to confirm a CKD diagnosis and identify its cause, but — importantly a diagnosis requires persistence or progression of the defining abnormality for ≥3 months. A single GFR value or albuminuria result is insufficient and, if used for diagnosis of CKD, may lead to a high false-positive rate for diagnosis**.** Progression is defined according to changes in eGFR by KDIGOn**(22).**

Estimating and measuring GFR. The assessment first begins with measurement of serum creatinine concentration under steady-state conditions and using formulae for estimating GFR (several of which are available, such as the CKD-EPI creatinine equation). The results of these creatinine-based tests can be influenced by changes in muscle bulk (atrophy or hypertrophy), dietary intake of cooked red meat and alterations in tubular secretion of creatinine owing to exposure to drugs (such as trimethoprim/sulfamethoxazole) **(6).**

Alternative approaches using serum cystatin C concentrations have also been proposed; although these are not influenced by muscle bulk and diet, the cystatin C-based formulae for eGFR can be affected by inflammation, obesity, thyroid disease, diabetes and steroid administration **(24).** Importantly, some eGFR formulae have not been extensively validated in older people and might not apply to people of Asian or African descent**(11).** Demographic variables of age and sex, which might be used to correct for differences in creatinine generation, might also create unwanted complications in determining prognostic implications of an eGFR. Newer eGFR formulae, such as the full age spectrum (FAS) equation, use serum creatinine, cystatin C or a combination of both and have improved accuracy**.** In certain circumstances, such as when stratifying long-term risks of unilateral nephrectomy for potential living kidney donors, measuring rather than estimating GFR can be useful**.** Although cumbersome and expensive, mGFR assessments using urinary clearance methodology can sometimes be needed. However, methods of plasma clearance of the contrast agent iohexol or of radiolabelled iothalamate could avoid some of these issues**(25).**

Measuring proteinuria. Abnormal urinary excretion of albumin or total protein is essential to detect CKD when GFR is normal and contributes to the assessment of prognosis**.** Proteinuria (or albuminuria) can be

determined in several ways, including simple dipstick qualitative methods, point-of-care urinary albumin concentration tests, random urine samples to calculate the urine protein to creatinine ratio (UPCR) or the urine albumin to creatinine ratio (UACR) or timed 24-hour urine collections to measure absolute protein or albumin excretion each have advantages and disadvantages. Despite some limitations, UACR and UPCR are widely used to assess proteinuria in spot urine samples, although qualitative dipstick values can be approximated to corresponding protein concentrations and predominate in primary care settings and LMICs. Urinary protein or albumin excretion are more variable than serum creatinine levels, and can be influenced by posture, activity, fever or drug use; accordingly, multiple specimens must be collected to enhance reliability. UPCR and UACR methods can be influenced by the prevailing urinary creatinine excretion rate; that is, low creatinine excretion (for example, in patients with sarcopenia) can increase UPCR or UACR values even at normal absolute protein or albumin excretion rates. Hence, adjusting for the effect of urinary creatinine excretion can enhance the accuracy of UPCR and UACR measurements**(26).**

In the KDIGO schema, UACR values are divided into three categories, namely, normal or moderately increased, moderately increased and severely increased. Even with a normal eGFR, CKD can be diagnosed with a persistent, moderately increased UACR of >30 mg per g. Each incremental increase in UACR is associated with an increased risk of mortality and ESRD, so sustained albuminuria (or proteinuria) is a powerful prognostic marker. Given that persistent proteinuria is a good predictor of the risk of CKD progression, albuminuria or proteinuria can enable detection of CKD. However, several forms of progressive CKD can present with normal or only slightly increased albuminuria or proteinuria, such as autosomal dominant polycystic kidney disease**.** Marked proteinuria (>3.5 g per day in adults), especially when accompanied by a reduction in serum albumin concentration (<3.5 g per dl) the so-called nephrotic syndrome nearly always implies a diagnosis of a primary or secondary glomerulopathy underlying CKD**(27).**

Biopsy and pathology. Percutaneous kidney biopsy is a valuable tool in assessing the underlying cause of CKD. The indications for renal biopsy in a patient with CKD depend on the potential benefits (precise diagnosis, prognostication or determination of appropriate therapy) and the risk of biopsy-related complications. The risks of renal biopsy are minimal in experienced hands, with complications being mostly related to bleeding after the procedure. Fatal complications are rare (about 1 in every 10,000–20,000 biopsies) and major complications, such as need for nephrectomy or blood transfusion, occur in about 0.7–1.8% of biopsies. Kidney biopsies are commonly recommended for adults with nephrotic syndrome but can also be indicated in those with unexplained, rapidly progressive loss of kidney function, persistent haematuria and low-grade proteinuria (0.5–3.0 g per day) or isolated proteinuria (1.0–3.0 g per day). Depending on the circumstances leading to the procedure, the pathological findings can vary widely; in those with marked proteinuria, glomerular diseases are most likely to be evident. The degree of tubulointerstitial scarring can provide useful prognostic information **(28).**

Other tests. Detection and determination of the cause of CKD also rely on renal imaging (ultrasonography, CT and MRI), careful examination of the urinary sediment and specialized biochemical and serological tests suitable to detect specific disorders that cause CKD. Imaging tests are particularly valuable as they provide information on kidney size, contours, location and density as well as information on the anatomy of the urinary drainage system (renal pelvis, ureters and bladder). Specific lesions, such as cysts, dilatation of ureters or pelvis, calcification, masses and scars can provide valuable clues to the cause of CKD or confirm a specific diagnosis (such as autosomal dominant polycystic kidney disease or obstructive uropathy)**.** Urine sediment examination is important to detect and quantify haematuria, leukocyturia and casts (which form in the distal tubules by aggregating components present in the tubule lumen such as tubular cells and debris, white blood cells, red blood cells, proteins and/or lipids into a glycoprotein matrix that is excreted into the urine). Genetic testing is also emerging as an important tool for determining the cause of CKD, particularly in children and young adults. Autosomal dominant polycystic kidney disease, podocytopathies causing steroid-resistant nephrotic syndrome, Fabry disease and Alport syndrome are well-known entities that can be diagnosed using genetic tests. Next-generation sequencing studies have revealed unexpected genetic heterogeneity as well as alterations in numerous different genes in a substantial proportion of patients with

these diseases (familial, syndromic and sporadic), suggesting the need to update the current diagnostic algorithms and therapeutic choices. Continuing advances in the field of serum and urine proteomics, microRNA biology and serology are providing new powerful and non-invasive tools to identify specific diseases or groups of diseases. These new tools might also expand prognostication beyond GFR and proteinuria estimation giving rise to exciting new possibilities for precision medicine tailored to the exact diagnostic and prognostic characteristics of each patient **(28).**

MANAGEMENT

Several aspects need to be considered when managing patients with CKD, including controlling further nephron injury, normalizing single-nephron hyperfiltration, controlling CKD-related complications and preparing the patient for kidney replacement therapy. At the core of these is the principle of 'the earlier, the better', which is the effort to reduce the progression to ESRD and optimize renal outcomes. To achieve this, a systems-level approach to patient and physician education has been undertaken by numerous organizations**(23).**

The benefits of early therapy are well documented for Alport syndrome**.** Initiating RAS blockade after a genetic diagnosis but before any signs of kidney disease can have dramatic effects on renal outcomes, whereas initiating RAS blockade once CKD G3 is evident only somewhat delays progression to ESRD**.** Further support comes from a post hoc analysis of clinical trial data of RAS blockade in diabetic kidney disease; the gain of ESRD-free years was highest when RAS blockade was initiated at the time of microalbuminuria identification and lowest when initiated once a diagnosis of CKD G3 or G4 was made. Thus, early diagnosis and treatment are essential to prevent nephron loss as early as possible **(29).**

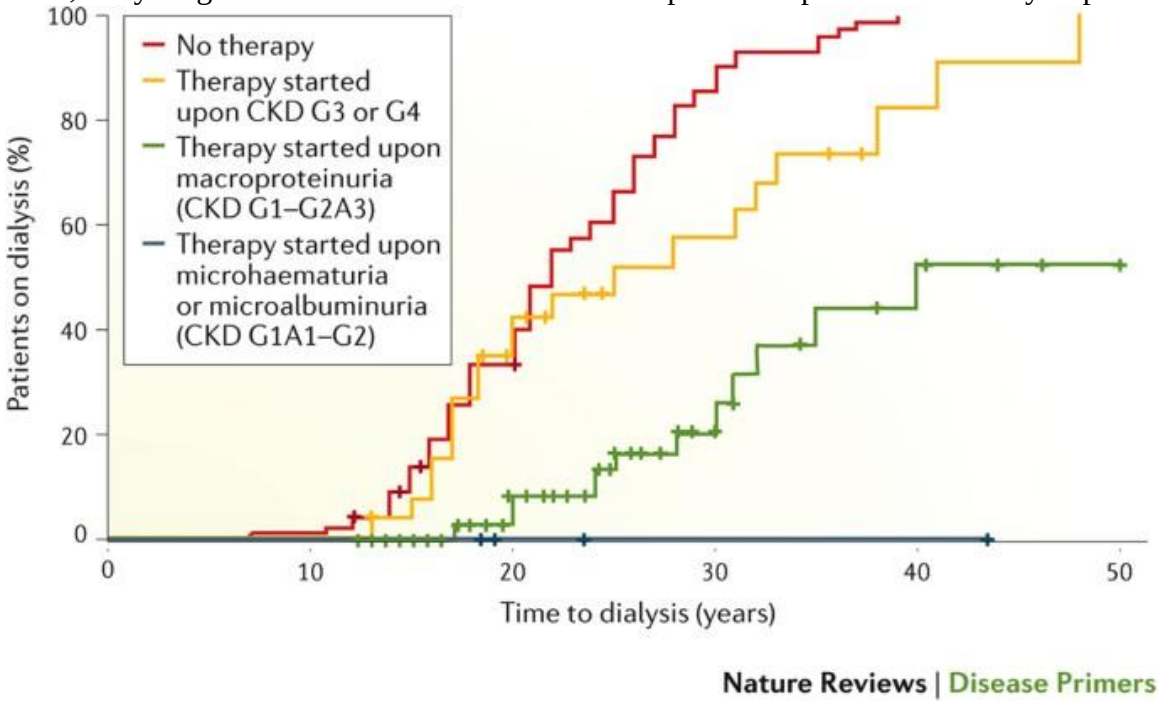

Figure 2: The earlier, the better.

In those with Alport syndrome, the time to renal replacement therapy was longest for those who started renin–angiotensin system (RAS) inhibition early, at the onset of microhaematuria (usually at birth) or microalbuminuria (30–300 mg protein per day or per g creatinine). Delaying until macroproteinuria was evident (>0.3 g protein per day or per g creatinine) or until chronic kidney disease (CKD) G3 or G4 was evident considerably shortens the time to renal replacement. 'No therapy' here represents relatives of the treated patients who have the same genotype **(23).**

Controlling ongoing nephron injury

Nephron injury can be driven by numerous triggers, and abrogating these triggers will slow progression to CKD and ESRD. Specific cures for genetic kidney diseases exist and are mostly limited to enzyme replacement therapy or substrate supplementation. The genetic basis of immune-mediated nephron injury is

not yet fully explored, but progression of CKD associated with C3 glomerulonephritis or atypical haemolytic uraemic syndrome can be controlled with complement inhibitors. Most acute forms of immune-mediated nephron injury present either as vasculitis, immune complex glomerulonephritis or interstitial nephritis (including allograft rejection). These disorders can often be targeted with immunomodulatory drugs (and sometimes with plasma exchange) to limit nephron loss from attack by the humoral and/or cellular elements of the immune system **(30).**

By contrast, in smouldering immune injury, such as in chronic IgA nephropathy, it is difficult to dissect CKD progression driven by immune versus non-immune mechanisms and the effectiveness of immunosuppression versus RAS blockade and blood pressure control is less evident. Kidney biopsy can establish the underlying diagnosis and guide management by assessing the ongoing activity of immune injury versus irreversible damage in, for example, lupus nephritis, IgA nephropathy or allograft dysfunction. Specific treatments are also available for CKD related to urinary tract obstruction, infections and some forms of toxic injury. However, even with complete abrogation of the injurious trigger, recovery of lost nephrons is impossible**(22).**

Avoiding further episodes of AKI is crucial to minimize stress on the remnant nephrons in CKD. This implies patient education on avoidable nephrotoxins (such as large volumes of radio contrast media, NSAIDs, certain antibiotics, possibly proton pump inhibitors or other endemic or occupational toxins). Hypovolaemic states as well as urinary outflow obstruction should be avoided. Additionally, asymptomatic leukocyturia alone might not imply bacterial infection, and antibiotic treatment should be limited to cases in which dysuria, bacteriuria and leukocyturia indicate infection. Smoking cessation is essential to minimize CVD**(31).**

Normalizing single-nephron hyperfiltration

Rigorous RAS inhibition with angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARBs) has the capacity to substantially reduce $GFR_{(single\text{-}nephron)}$ and glomerular filtration pressure, which leads to a decline in not only proteinuria but also total GFR — and, hence, moderately increases serum creatinine levels**.** At first, this serum creatinine increase is worrisome to patients (and physicians) and requires clarification that reducing hyperfiltration in remnant nephrons is the central strategy to retard CKD progression in patients with proteinuria. By contrast, ACEi or ARBs do not retard the progression of non-proteinuric forms of CKD such as autosomal dominant polycystic kidney disease but might benefit on the associated cardiovascular complications **(32).**

ACEi or ARBs should be titrated to the maximal possible dose, whereas hyperkalaemia can be corrected using loop diuretics (which act at the ascending limb of the loop of Henle) or potassium-binding resins**(.** A moderate increase in serum creatinine levels indicates a decline in $GFR_{(single\text{-}nephron)}$, which is a powerful predictor of the intended nephroprotective effect. Numerous randomized clinical trials have documented that RAS inhibitors can retard or even halt CKD progression. Reducing dietary salt and drugs that support the control of blood pressure and hyperlipidaemia, often referred to as the 'remission clinic protocol', can further reduce proteinuria and retard CKD progression. Such interventions are affordable and are essential when kidney replacement therapy is not available or affordable **(33).**

Next, blood pressure targets remain an area of debate. A subgroup analysis of the Systolic Blood Pressure Intervention Trial documented reduced rates of major cardiovascular events and all-cause death when a systolic blood pressure <120 mmHg was reached (compared with <140 mmHg) in patients with CKD and hypertension without diabetes. However, these effects might not apply to patients with CVD who are susceptible to compensatory neurohumoral stimulation and sudden cardiac death upon tight blood pressure control. Blood pressure target levels also depend on the method of blood pressure measurement**.** Finally, lifestyle modifications such as avoiding or correcting obesity can also reduce filtration load and glomerular hypertension; hence, a normal BMI is a treatment target to retard CKD progression**.** However, any immunosuppression-related benefit of using steroids in CKD can be counterbalanced by steroid-related obesity that drives glomerular hyperfiltration and secondary FSGS, which could explain why steroid treatment falls short in retarding progression of IgA nephropathy-related CKD**.** Additionally, concomitant diabetes has important implications for CKD management. Hyperglycaemia maximizes glomerular

hyperfiltration via SGLT2-driven vasodilation of the afferent arteriole of the remnant nephrons, which cannot be controlled by RAS inhibitors**.** Accordingly, SGLT2 inhibitors can reverse this process and elicit profound additive nephroprotective effects on CKD progression; their capacity to also reduce CVD in patients with type 2 diabetes provides a strong rationale for dual RAS and SGLT2 blockade in patients with diabetes and CKD **(34).**

Controlling CKD complications

CKD is associated with a number of secondary complications that require management, the most relevant of which in terms of overall mortality is CVD**.** Cardiac and vascular alterations also arise from endocrine failure (for example, a lack of erythropoietin, vitamin D or PTH), which causes anaemia and secondary hyperparathyroidism. Myocardial fibrosis is the final consequence of the multiple underlying causes**(35).**

Large randomized controlled trials in patients on haemodialysis have tested a number of different interventions intended to reduce cardiovascular events, including frequency and length of dialysis sessions and flux (filtration coefficient of the membrane in the dialyser), erythropoietin-stimulating agents, statins, RAS blockade, folic acid, cinacalcet (a calcium mimetic used to treat secondary hyperparathyroidism) or vitamin D derivatives but have largely been unsuccessful**.** For example, reduction of low-density lipoprotein cholesterol with simvastatin (a statin) plus ezetimibe (which decreases cholesterol absorption) reduced the incidence of major atherosclerotic events more efficiently in patients with CKD G2–G4 than in patients with CKD G5 or who were on dialysis. Guideline-directed approaches on the basis of diabetic status aim to achieve target blood pressure through administration of RAS blockers, salt restriction and anaemia prevention**(36).**

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