REVIEW ARTICLE

Chronic Kidney Disease

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SUMMARY

Chronic kidney disease is highly prevalent (10-13% of the population), irreversible, progressive, and associated with higher cardiovascular risk. Patients with this pathology remain asymptomatic most of the time, presenting the complications typical of renal dysfunction only in more advanced stages. Its treatment can be conservative (patients without indication for dialysis, usually those with glomerular filtration rate above 15 ml/minute) or replacement therapy (hemodialysis, peritoneal dialysis, and kidney transplantation). The objectives of the conservative treatment for chronic kidney disease are to slow down the progression of kidney dysfunction, treat complications (anemia, bone diseases, cardiovascular diseases), vaccination for hepatitis B, and preparation for kidney replacement therapy.

KEYWORDS: *Conservative Kidney Management. Chronic Kidney Disease End Stage. Renal Failure.*

DEFINITION

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 represents 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 m^2, or GFR greater than 60 ml/min/1.73 m^2, 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 [1]. 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.

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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:[2]

TABLE 1. CKD STAGE; GFR = GLOMERULAR FILTRATION RATE.

Stages	GFR value ml/min/1.73m2	Classification
I	>90	Normal or High
II	60-89	Slightly decreased
III A	45-59	Mild to moderately decreased
III B	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.

Category	24-Hour Albuminuria mg/24 h	A/C Ratio Mg/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.

It is worth remembering that albuminuria between 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:

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

		Albuminuria		
	GFR	<30 mg/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.

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 advantage of an early diagnosis is to facilitate the adjustment of medication dose and allow better preparation for renal replacement therapy if indicated[3].

The presence of the following risk factors determines the screening for CKD in adults[4]:

- History of diabetes, hypertension, cardiovascular disease (CVD), human immunodeficiency virus (HIV) or hepatitis C virus infection, malignancy, autoimmune diseases, nephrolithiasis, or recurrent urinary tract infections.
- Family history of renal disease.

Patients selected for CKD assessment should undergo:

- 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[5];
- Imaging exam, particularly an ultrasound of the kidney and urinary tract.

Some practical aspects of detecting CKD should be remembered[6]:

- 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[7]. In Brasil, estimates of the prevalence of the disease are uncertain[8]. 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[9]. 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 million population (pmp) was 610[10].

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 cardiovascular causes, while 0.96 million were related to end-stage renal disease[11]. The aforementioned SBN census found a gross annual mortality rate of 19.9% on dialysis.

REFERRAL TO A NEPHROLOGIST

The referral of patients with chronic renal dysfunction to a nephrologist varies according to the characteristics of the health care system of each region, which are oftentimes not uniform, even in the same country. However, the following characteristics usually indicate the necessity of follow-up with a nephrologist[12]:

1. GFR <30 mL/min/1.73 m^2.

2. A decrease greater than or equal to 25% in the GFR.

3. Progression of the CKD with a sustained decrease in the GRF of more than 5 ml/min per year.

4. A consistent finding of significant albuminuria.

5. Persistent unexplained hematuria.

6. Secondary hyperparathyroidism, persistent metabolic acidosis, anemia due to a erythropoietin deficiency.

7. Hypertension resistant to treatment with four or more antihypertensive agents.

8. Persistent abnormalities of serum potassium.

9. Recurrent or extensive nephrolithiasis.

10. Hereditary kidney disease or unknown cause of CKD.

ROUTINE TREATMENT AND MANAGEMENT

The care of CKD patients includes:
- slowing the progression of CKD;
- treat complications related to the pathology, such as anemia, mineral and bone disorder, hydroelectrolytic disorders, metabolic acidosis, and cardiovascular disease;
- prepare the patient for renal replacement therapy (RRT);
- establish a immunization routine, especially for hepatitis B.

It is important to highlight that, in all levels of treatment, it is necessary to have a multidisciplinary team, particularly of nutrition, nursing, psychology, and social assistance.

Routine for the assessment and management of CKD progression

The evaluation of CKD progression is based on the evaluation of three aspects: decline in renal function in patients who were monitored in a longitudinal way with comparable methods; occurrence of renal failure, defined by the initiation of RRT; symptoms or complications of decrease of renal function and the development or worsening of proteinuria, particularly in diabetic nephropathy[1,2].

Data from the literature with approximately two years of follow-up of patients with CKD show that the average decrease in the glomerular filtration rate was 4-5 mL/min/year and that 85% of the patients had this average decline[13]. Therefore, we must periodically evaluate the decrease of the glomerular filtration rate (GFR), and consider a decrease greater than 5 ml/min/1.73 m^2/year[2] to be an indicator of accelerated progression. In Table 4, we suggest a frequency of monitoring; however, this scheme should be tailored according to the clinical status of the patient and the underlying renal disease.

TABLE 4. FREQUENCY OF FOLLOW-UP (NUMBER OF TIMES PER YEAR), ACCORDING TO THE GFR AND LEVEL OF ALBUMINURIA (ADAPTED FROM 3); GFR: GLOMERULAR FILTRATION RATE IN ML/MIN/1.73 M².

		Albuminuria		
	GFR	<30 mg/g	30-300 mg/g	>300 mg/g
Stage 1	≥90	1 if CKD	1	2
Stage 2	60-89	1 if CKD	1	2
Stage 3A	45-59	1	2	3
Stage 3B	30-44	2	3	3
Stage 4	15-29	3	3	4 or more
Stage 5	<15	4 or more	4 or more	4 or more

In general, the strategies used to reduce the progression of CKD are:

- use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers for patients with proteinuria above 500 mg/24 hours;
- reach target blood pressure below 130x80 mmHg;
- reach levels of glycated hemoglobin lower than 7% for diabetic patients;
- protein restriction indicated and managed by a nutritionist;
- correction of metabolic acidosis;
- stimulation for smoking cessation.

In addition, it is essential to assess the presence of factors of exacerbation of CKD, such as volume depletion, use of nephrotoxic substances, such as iodinated contrast, antibiotics, non-steroidal anti-inflammatory drugs, and obstruction of the urinary tract.

Routine for the evaluation of anemia in CKD

Anemia is a frequent complication in individuals with CKD[14], and the erythropoietin deficiency is its most common factor, together with iron, folic acid, and vitamin B12 deficiency. Therefore, it is part of the routine treatment of CKD patients to investigate the presence of anemia and indicate and follow-up its treatment.

For patients without anemia, the hemoglobin concentration should be requested when clinically indicated or according to the suggestion presented in Table 5[14].

For patients with anemia, defined by hemoglobin lower than 13 g/dl for men and 12 for women[14], hemoglobin concentration tests should be requested when clinically indicated or every three months for patients in stages III to V of CKD.

For patients under treatment for anemia with iron replacement and/or using erythropoiesis-stimulating agents, the hemoglobin and iron control must be done at every patient consultation or at least every three months.

Routine for the evaluation of mineral and bone disorder in CKD

Mineral and bone disorder in CKD is defined as a set of changes in the mineral metabolism of CKD patients, including renal osteodystrophy, a histological manifestation of the disease.

To diagnose mineral and bone disorder in CKD, it is necessary to determine the serum levels of calcium, phosphorus, alkaline phosphatase, and intact parathyroid hormone (PTH), in addition to venous blood gas. These examinations should be performed in all CKD patients with GFR below 60 ml/min/1.73 m². The frequency of the exams must be based on the stage and risk of progression of CKD, as suggested in Table 5[15].

Another aspect that could be part of the routine treatment is the assessment of vitamin D deficiency since its incidence is high in CKD under conservative treatment[16] and is associated with the progression of hyperparathyroidism, lower bone mineral density, and risk of fractures[17,18]. In addition, vitamin D deficiency has been associated with changes in the immune response, insulin resistance, changes in vascular function, and cardiomyopathy[19].

Routine for the evaluation of metabolic acidosis and electrolytic changes in CKD

Metabolic acidosis occurs in most CKD patients when the glomerular filtration rate is less than 30 ml/min[20]. It is usually mild to moderate, with bicarbonate ranging between 12 and 22 mEq/L.

The benefits of correcting metabolic acidosis have been described in the literature. In fact, Brito-Ashurst and col.[21] evaluated 134 patients with CKD (creatinine clearance of 15 to 30 ml/min/1.73 m²) and serum bicarbonate between 16 and 20 mmol/L and found that the supplementation with bicarbonate slowed progression to the final stages of CKD, as well as improving the nutritional status of patients.

The determination of bicarbonate should be routinely done according to the stage of CKD, and the target level of bicarbonate must be greater than or equal to 22 mEq/L; alkaline salts should be used to achieve this target.

The main electrolyte disorder in CKD patients under conservative treatment is hyperkalemia.

The measurement of potassium levels should be done at every patient consultation, and, when hyperkalemia is detected, it is important to assess errors in diet, medications that can lead to hyperkalemia, the presence of metabolic acidosis, and question the use or dose increase of potassium-sparing diuretics.

Routine for the evaluation of cardiovascular disease in CKD

Cardiovascular disease (CVD) is the main cause of morbidity and mortality among the population with CKD[22]. Based on data from the literature, all patients with CKD should be considered at high risk for CVD, evaluated based on "traditional" and "non-traditional" (related to uremia) risk factors for CVD, and treated for the reduction of modifiable cardiovascular risk factors[23].

The following can be established as routine identification of CVD in these patients: yearly electrocardiogram and echocardiogram, and non-invasive tests, such as myocardial scintigraphy or stress echocardiography for patients who are symptomatic or have changes in segmental motility, with three or more traditional risk factors, or with a history of peripheral vascular insufficiency and cerebral vascular accident. In the presence of clinical symptoms and positive results in invasive or non-invasive exams, it is recommended to refer the patient to a specialized cardiac assessment.

In addition to identifying CVD, it is important to establish strategies to reduce risk factors, such as control of hypertension and diabetes, dyslipidemia assessment, smoking cessation, stimulation of physical exercises, treatment of anemia, and reduction of proteinuria levels.

Routine for hepatitis B immunization in CKD

According to the 2012 dialysis census by the SBN, the prevalence of hepatitis B in patients undergoing hemodialysis in Brasil is 1%. The correct application of a vaccination scheme is one of the main factors responsible for the reduction in the incidence of this infection in dialysis. It is worth pointing out that the response to vaccination in this population varies from 40% to 60%, and that the maintenance of the antibodies titer is not sustained. It is important to establish a routine vaccination for non-immune patients. One of the proposed schemes carried out in basic health units is to make four applications with a double dose (4 ml) of Engedrix B© on the deltoid muscle in months 0, 1, 2, and 6. After 30 days of the end of the scheme, the AntiHbs are monitored - if lower than 10 miu/ml, a booster dose is recommended with a double dose (4 ml) of Engedrix B©; the maximum booster doses allowed are three.

Routine to prepare for renal replacement therapy

The decision to start dialysis in a CKD patient involves considering subjective and objectives parameters by the physician and patient. There are no absolute laboratory values that indicate a requirement to begin dialysis. The following are considered when deciding to initiate RRT: aspects of quality of life, psychological aspects associated with the anxiety of undergoing complex therapy, the perception of the nephrologist on the health state of the patient, the decline of renal function, and the risks associated with renal replacement therapy.

In the follow-up of CDK patients that present a progressive decrease of renal function and in those with GFR less than 20 ml/min, it is essential to address the types of RRT, along with their Indications, advantages, and disadvantages. Once the patient has opted for a particular type of RRT and provided there are no medical contraindications, it is necessary to initiate the appropriate preparations, especially the manufacturing of the arteriovenous fistula for hemodialysis, peritoneal dialysis training, implantation of the Tenckhoff catheter, serology for hepatitis B, C, and HIV. If the patient is interested and meets the clinical conditions, they can also be forwarded to outpatient clinics specialized in pre-renal transplantation evaluation.

As soon as the patient presents very reduced GFR and/or compatible symptoms, such as nausea, vomiting, drowsiness, weight loss, hiccups, among others, we must request RRT to the competent organs of the Single Health System or through complementary medical services. It is important to emphasize that if these symptoms are accentuated or if there are changes in laboratory findings that indicate high risk, the patient must be referred to the urgent start of RRT.

In Table 5, we suggest a model of test grouping according to the risk of progression of CKD.

TABLE 5. ROUTINE OF EXAMS ACCORDING TO THE RISK OF PROGRESSION OF CKD.

Department	Low	Moderate	High	Very high
Renal function				
GFR	Every consultation	Every consultation	Every consultation	Every consultation
Urine 1	Yearly	Every six months	Every six months	Every six months
Proteinuria	Yearly	Every six months	Every six months	Every six months
Anemia				
Complete blood count	Yearly	Every six months	Every consultation	Every consultation
Iron	-	Every six months	Quarterly #	Quarterly #
Transferrin	-	Every six months	Quarterly #	Quarterly #
Ferritin	-	Every six months	Quarterly #	Quarterly #
Bone disease				
Ionized calcium	Yearly	Every six months	Quarterly	Every consultation
Phosphorus	Yearly	Every six months	Quarterly	Every consultation
PTH	-	Yearly	Every six months	Quarterly #
Metabolism				
Cholesterol	Yearly	CV Risk*	CV Risk*	CV Risk*
Triglycerides	Yearly	CV Risk*	CV Risk*	CV Risk*
Uric acid	Yearly	Every six months	Every six months	Every six months
Venous blood gas	-	Yearly	Quarterly	Every consultation
Glycemia	Yearly	If diabetes	Quarterly	Every consultation
Hb1Ac	-	If diabetes	Quarterly	Quarterly
TGO, TGP; CPK	Consultation[&]	Consultation[&]	Consultation[&]	Consultation[&]
Nutrition				
Urea clearance	-	Every six months	Quarterly	Bimonthly
Urine Sodium	Yearly	Every six months	Every six months	Every six months
Potassium	Yearly	Every consultation	Every consultation	Every consultation
Viral profile				
HbsAg	-	Yearly	Yearly	Dialysis**
Anti-HbsAg	-	Yearly	Yearly	Dialysis**
Anti-Hbc	-	Yearly	Yearly	Dialysis**
Anti-HIV	-			Dialysis**
Anti-HCV	-			Dialysis**
Others				
Echocardiogram	Yearly	Yearly	Yearly	Yearly

GFR = estimated glomerular filtration rate or by 24-hour urine creatinine clearance; # if treatment; * according to the cardiovascular risk; ** at the moment of referral to dialysis; [&] if under treatment with statins or fibrates.

CONCLUSION

Chronic renal disease has an important impact on the morbidity and mortality of patients. The organization of the conservative treatment is crucial to slow the progression of kidney dysfunction, as well as to lessen the occurrence of complications, with a positive impact on the prognosis of the affected population. Another important aspect is the preparation for renal replacement treatment, which greatly facilitates the adaptation of patients to the chosen therapy.

PALAVRAS-CHAVE: *Doença renal crônica. Doença renal crônica estágio final. Tratamento conservador.*

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