

Fast Reading of the KDIGO 2012: Guidelines for evaluation and management of chronic kidney disease in clinical practice

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ABSTRACT

The authors of this "fast reading" present the data they have considered as more relevant in the KDIGO 2012 as concerned to evaluation and management of chronic kidney disease. The text does not correspond to their opinion, it is a brief presentation of guidelines that could be useful in clinical practice.

Keywords: anemia; creatinine; glomerular filtration rate; kidney failure, chronic.

INTRODUCTION

A new version of chronic kidney disease (CKD) Guidelines, developed by KDIGO, was published in early 2013. The definition of CKD - kidney structural and/or functional abnormalities present for more than three months - was maintained; and the words "with health implications" were added. The purpose of such change was to stress that there may be a variety of abnormalities in kidney structure and function; however, not all of them have undesirable clinical implications for an individual's health, and thus need to be properly contextualized.

In the new version of the CKD Guidelines, they recommend to classify the disease based on the cause, in the glomerular filtration rate (GFR) class and albuminuria (Chart 1), which enables the physician to identify the risks of adverse outcomes related to the renal impairment and death. They highlight the importance of establishing the cause of CKD - which is important to decide

on the specific treatment in order to change risk estimates.

The instruction to estimate GFR from serum creatinine as the best method for the diagnosis, classification and treatment of CKD progression was maintained. The GFR (in mL/min/1.73 m²) was divided into the classes G1 (> 89), G2 (60-89), G3a (45-60), G3b (30-44), G4 (15-29) and G5 (< 15).

They recommend the CKD-EPI equation to estimate GFR and they underscore the need to resort to other methods to confirm the diagnosis of CKD. For instance, KDIGO recommends CKD diagnostic confirmation in adults with estimated GFR (eGFR) between 45-59 mL/min/1.73 m² without other renal parenchyma lesions - either using serum cystatin C dosing, or possibly by means of a more specific test (e.g. exogenous markers of glomerular filtration).

Proteinuria or albuminuria (ideally expressed as mg/g of creatinine) was divided into A1 (or normal or slightly increased, when < 30 mg/g); A2 (or moderately increased in the range of 30-300) and A3 (or markedly increased to values > 300 mg/g) - terminology replacing normoalbuminuria, microalbuminuria and macroalbuminuria, previously adopted.

The big news of current CKD guidelines refers to the prominence given to the risk of adverse outcomes of the disease, based on the cause, the GFR, the amount of albuminuria and other concomitant medical conditions, from the work of the "CKD Prognosis

CHART 1 LIKELIHOOD OF CHRONIC KIDNEY DISEASE, BASED ON CAUSE, GLOMERULAR FILTRATION RATE AND ALBUMINURIA

Cause	Category	eGFR*	Albuminuria (proteinuria)**		
*Glomerular disease	1	≥ 90	A1 (< 30)	A2 (30-300)	A3 (> 300)
*Tubular-interstitial disease	2	60-89	-	+	++
*Vascular disease	3a	45-59	+	++	+++
	3b	30-45	++	+++	+++
*Congenital disease	4	15-29	+++	+++	+++
*Cystic disease	5	< 15	+++	+++	+++

* eGFR: Estimated glomerular filtration rate in mL/min/1.73 m²; ** mg/g of creatinine. Risk for CKD: (-): Low risk (no CKD if there are no other markers of kidney injury); (+): Moderately increased risk; (++) : High risk; (+++) : Very high risk.

Consortium”, which evaluated data from 45 cohorts in a total of 1,555,332 participants. Disease prognosis situations are presented, with the probabilities of outcomes, such as mortality from all causes, cardiovascular mortality, progressive CKD, need for renal replacement therapy (RRT) and the impact of acute kidney injury in renal functional loss in the long run. Based on these situations, one can infer whether a patient has a greater or lower chance of, for instance, lose kidney function and require RRT. Thus, 70-year-old male with a GFR of 50 mL/min/1.73 m² and without albuminuria (G3a/A1- according to the new classification) has a lower likelihood of needing RRT than a patient of 55 years with a GFR of 70 mL/min/1.73 m²; albuminuria of 1.5 g/day (G2/A3). For example, in the case of the 70-year-old gentleman, more attention should be paid to the cardiovascular complications and less to the CKD progression.

Chart 1 chronic kidney disease probability, based on the cause, on the glomerular filtration rate and on albuminuria.

CKD DIAGNOSIS

They reinforce criteria to be used for CKD diagnosis, which are presented on Table 1.

Throughout the Guidelines, the authors also present adjustments to the criteria to be adopted for children (considering the particularities of this group from birth to 18 years of age), whose reference ranges of laboratory results are differentiated.

It is important to remember that chronicity is not synonymous with irreversibility; therefore, the Guidelines take into account that some CKD cases may be reversible either spontaneously or with treatment.

TABLE 1 CKD CRITERIA (ANY ONE OF THE FOLLOWING FOR MORE THAN 3 MONTHS)

Kidney injury markers (one or more):
Albuminuria (> 30 mg/24h; creatinine/albumin ratio 30 mg/g)
Abnormalities in urinary sediment
Electrolyte and other unbalances caused by tubular lesions
Abnormalities detected by histological exam
Structural abnormalities detected by image exam
Kidney transplant
Reduced GFR:
< 60 ml/min/1.73 m ² (GFR categories G3a-G5)

Regarding renal function assessment, GFR - a component of the excretion function of the kidneys, is accepted as the best index for functional assessment, although the kidneys have many other functions, including endocrine and metabolic.

With regard to renal function markers, GFR estimates based on serum creatinine; but not serum creatinine alone, are sensitive enough to detect the measured GFR < 60 ml/min/1.73 m², and can be confirmed by estimates using alternative markers or true GFR measures, if necessary. For various reasons, focus has shifted from proteinuria quantification into albuminuria (but not microalbuminuria). Albuminuria is the main component of urinary protein in most renal diseases, with which there has been a strong relationship with the kidney and cardiovascular risks. Albuminuria is a common finding, but it is not uniform in CKD.

Since 2002, several epidemiological studies have associated reduced GFR and albuminuria to the risk of adverse outcomes - which had not been previously considered CKD complications. Due to its

high prevalence, adverse outcomes and high costs of CKD, especially kidney failure, some countries have developed public healthcare programs for early detection and treatment of CKD and its complications, and the effectiveness of these programs is under assessment.

Structural and functional kidney abnormalities may not have implications on the health of the individual and therefore need to be contextualized. One should always consider factors specific to each case and not stagnant values from test results. It is noteworthy that epidemiological studies have shown an increased prevalence of reduced eGFR and increased albuminuria/creatininuria ratio in older individuals; however, it is unclear whether this is in fact the disease or if it results from “normal aging”. Numerous studies have shown histopathological abnormalities associated with aging, including glomerular sclerosis, tubular atrophy and vascular sclerosis. Regardless of the cause, these two conditions seem to be associated with increased risk of cardiovascular disease.

It is interesting to remember that healthy older individuals (without comorbidities) do not necessarily have diminished GFR; and levels lower than 60 ml/min/1.73 m² are the exception.

Among the special circumstances relating to GFR, we stress the kidney donor, whose usual level of GFR after donation is approximately 70% of the pre-donation value - which is in the range of 60-90 ml/min/1.73 m² for most donors. When it is less than 60 ml/min/1.73 m², there is a need for careful monitoring.

GFR is also affected by protein intake. Healthy adults with low protein intake may have lower GFR, but they usually have GFR < 60 ml/min/1.73 m².

Albuminuria alone, without reduced GFR, may occur transiently in conditions other than CKD. It is considered that patients with persistent albuminuria have CKD. Albuminuria can be associated with obesity and metabolic syndrome, and remit with weight loss.

To prevent test interpretation to become highly complex, we adopted the albuminuria/creatinine threshold of 30 mg/g or about 3 mg/mmol, without corrections for gender and variations in creatinine excretion in order to detect diabetic nephropathy.

It is interesting to notice that there is an increased risk for higher levels of albuminuria in all GFR categories without a clear threshold. Three categories of albuminuria are adopted, but it is known that the classification is arbitrary, since the risk related with albuminuria is continuous. It is accepted that proteinuria in the nephrotic range confers additional risks.

However; the definition of GFR categories was deliberately based on the concept of “true” GFR; however, in research and clinical practice they have predominantly used GFR estimates based on serum creatinine, which can cause inaccuracies, including outcome differentiation between G1 (> 90 ml/min/1.73 m²) and G2 (60-89 ml/min/1.73 m²) ranges. Studies with cystatin C found prognostic gradients with eGFR levels above 60 ml/min/1.73 m², supporting a role for both GFR categories in the CKD classification.

Albuminuria categories are “broader” in relation to risk, with significant gradients within each category, with only three proposals in these guidelines, as per stated above, given the need to simplify their implementation in clinical practice.

METHODS TO ESTIMATE AND MEASURE RENAL FUNCTION

It is important that clinicians know several methods to estimate and measure kidney function and the situations in which specific methods may be superior in decision making regarding treatment and referral.

In general, GFR estimates may be used and in situations that are likely to be infrequent, and measurement may be necessary as in the evaluation of donor kidney function and in the use of toxic drugs with narrow therapeutic range.

It is recognized that no serum-creatinine-based equation will have great performance in all clinical circumstances and that there may be changes in the performance of estimation equations over time and in different regions. It is emphasized that, for purposes of releasing estimated GFR results, it is important to select a single equation in a region or country. In North America, Europe and Australia, the advantages of the CKD-EPI equation at higher GFR ranges make it more relevant than the MDRD-study equation for general practice and public health care.

It was commented that cystatin C use in eGFR equations would have some advantages over serum creatinine, but the test cost and potential lack of standardization between laboratories limit its recommendation as preferential and even as a second test after serum creatinine.

In regards to the assessment of albuminuria, it is suggested that the following measures for initial testing of proteinuria be used, giving preference to the first urine sample of the morning (2B), in this order:

1. Albumin/creatinine ratio in urine (UACR);
2. Protein/creatinine ratio (PCR);
3. Urinalysis reagent strip for total protein with automatic reader;
4. Urinalysis reagent strip for total protein with manual reading.

It is recommended that clinical laboratories provide UACR and PCR in untimed samples of urine instead of isolated albuminuria and proteinuria (1B) results. Moreover, one should not over use the term “microalbuminuria”.

For proteinuria, the reference test is the 24-hour urine dosage, knowing; however, that it is difficult to control the procedure and inaccuracies in urine collection may contribute to errors in protein loss estimation.

It is noteworthy that in children, PRC is the best choice when compared to the UACR. For adults, albuminuria is considered more appropriate, which best predicts adverse outcomes.

Unlike in adults, in whom the CKD is predominantly attributed to glomerular disease or hypertensive lesion, most children have underlying condition such as congenital anomalies of the kidneys and the urinary tract. Thus, the relative scarcity of glomerular diseases in children makes the albuminuria test less sensitive for diagnostic purposes, since many children have underlying tubular diseases and tend to excrete more Tamm-Horsfall and other low-molecular-weight proteins that will not be shown by albuminuria detection tests.

CKD PROGRESS EVALUATION

Lower GFR and higher albuminuria are both associated with and increased progression rate and are synergistic. More frequent measurements of estimated GFR and albuminuria should be considered

in patients with lower GFR and higher albuminuria because of the greater likelihood of progression.

The frequency of assessments should be individualized based on the patient’s history and underlying causes of kidney disease. Under specific conditions, such as glomerulonephritis or increased levels of albuminuria, assessments should be carried out more frequently (every 1-3 months).

Another approach to progression takes into account the rate of change in kidney function based on the analysis of the creatinine “slope”, assessing the loss by changes in the absolute and relative rates. Less than 25% change between two GFR estimates may reflect physiological variation more than true disease progress.

GFR and albuminuria should be monitored at regular intervals to identify declining rates that exceed those normally observed. The GFR decline rate may be relatively constant over time in an individual.

Clinicians are encouraged to evaluate changes in GFR and albuminuria in the context of multiple observations over time and pay attention to clinical events that might impact these changes.

Repeated measurements of serum creatinine over time are less likely to contribute to the assessment of children when compared to adults, primarily by changes in muscle mass that occur in growing children.

Some factors that may predict CKD progression are modifiable, such as lifestyle changes (stop smoking and avoid obesity) and measures such as lowering blood pressure, albuminuria reduction and hyperglycemia prevention. It can also be changed based on the underlying causes of CKD, since various causes can respond to a specific treatment, which should be considered in the first step (for example, immunosuppression).

CKD ASSESSMENT

CHRONICITY EVALUATION

- In people with GFR < 60 ml/min/1.73 m² (G3a-G5) or markers of kidney injury, history and prior measurements should be reviewed to establish the kidney disease duration (no rating).

- CKD is confirmed if the duration is > 3 months. One must follow the recommendations for CKD;
- If the length is not > 3 months or has not been established, CKD is not confirmed. Patients may have CKD or AKI or both, and the tests should be repeated.

Here, we are dealing with a definitive diagnosis of CKD with older measurements of renal function markers, proteinuria, imaging/ultrasound scans, biopsies, and other means.

Dosages should be repeated within a 3-month period and after that, to be sure about the CKD. The chronicity of this period cannot be established because the AKI may have such behavior.

EVALUATION OF THE CAUSE

- One should evaluate the clinical context, including personal and family history, environmental factors, medications, physical examination, laboratory tests, imaging exams and histopathological diagnoses to determine the kidney disease causes (no rating).

We need to establish the CKD cause, using standard clinical methods (attention to the differential diagnoses of hypertension and diabetes).

PEDIATRIC CONSIDERATIONS

In the case of a child with GFR < 60 ml/min/1.73 m² or one standard deviation below the expected level for their age and gender, one should follow the guidelines established for adult patients. We must remember that kidney development abnormalities account for 30% to 50% of the causes of CKD in children.

GFR EVALUATION

KDIGO emphasizes the robust estimates of GFR determination, using standardized measures of creatinine, but it also emphasizes cystatin C measurement.

- The use of serum creatinine and its clearance is recommended to obtain the estimated GFR for initial investigation (1A);
- Additional tests are suggested (such as cystatin C or its clearance) as confirmatory tests in specific circumstances when the GFR based on serum creatinine is less reliable (2B)."

There is no need to describe the estimated GFR using serum creatinine, considered good and robust. On the other hand, KDIGO describes the kidney function alternative assessment with cystatin C or its clearance.

PEDIATRIC CONSIDERATIONS

For children, we should prefer the clearance estimate instead of the simple use of serum creatinine on initial assessments, especially after the development of the equation that incorporates the child's height (Schwartz GI, 2009).

It is recommended that clinicians should (1B):

Use the GFR estimation equation derived from serum creatinine (eGFR) in place of serum creatinine alone;

Master the clinical situations where eGFR is less reliable.

GFR estimates were developed in serum creatinine stability/balance situations. We know that its serum levels is dependent on several factors, such as muscle generation, diet, tubular secretion and extra-renal elimination from the gastrointestinal tract, factors that are not considered determinants of GFR.

When setting up a GFR estimation equation using a population, these non-determinant factors are included in obtaining the GFR, balancing their relative importance, i.e. they are computed with their effects, so that the eGFR results are better than pure measurement of serum creatinine, which may have been influenced to a greater degree by one or more GFR non-determinant factors. In other words, the eGFR is balanced by the mean population of the GFR non-determinant factors. Of course, in creatinine instability situations, errors in estimated GFR are larger.

PEDIATRIC CONSIDERATIONS

These recommendations are fully applicable in pediatrics.

Clinical laboratories should (1B):

- Dose serum creatinine using a specific assay with calibration related to the international reference and comparable with minimum methodology bias that uses isotope dilution mass spectrometry (IDMS);
- Include the eGFR in the report, together with the adult serum creatinine and specify the equation used;

- Include the adult eGFR in the report using the 2009 CKD-EPI equation.
- If there is another equation, it is recommended that it be mentioned and it should have better accuracy compared to the CKD-EPI;
- Regarding serum creatinine, it is recommended that their results are rounded to the nearest integer (mmol/l) or the 100th integer in conventional units (mg/dl);
- By including the eGFR in the report, it is recommended that it should be rounded up to the nearest integer and be associated to the body surface area of 1.73 m² in adults, using ml/min/1.73 m² units;
- It is recommended that eGFR < 60 ml/min be reported as decreased.

It is important to relate eGFR to the body surface, because it keeps a balanced ratio between GFR and kidney size. It should be remembered that 1.73 m² of body surface area corresponded to the mean body surface area of 25-year-old men and women from the U.S. in 1927. It is also important to keep in mind that drugs today are adjusted for GFR unrelated to body surface. There are no accurate studies on which correction would be better (with or without body surface).

PEDIATRIC CONSIDERATIONS

- The eGFR should be reported only when the height of the child is known to the laboratory.
- The laboratory shall report eGFR values < 60 ml/min as reduced only in children over 2 years of age.
- Cystatin C should be dosed in adults with eGFR 45-59 ml/min/1.73 m² that have no marker of kidney damage when CKD confirmation is required (2C).
- If eGFR_{cys}/eGFR_{creat-cys} is < 60 mL/min, CKD diagnosis is confirmed;
- If eGFR_{cys}/eGFR_{creat-cys} is > 60 ml/min, CKD diagnosis is not confirmed.

There is evidence that cystatin C GFR estimates are better to predict mortality and cardiovascular events than estimates using creatinine. This is most apparent for clearances > 45 ml/min. Using the two formulas for obtaining clearance (cystatin C and serum creatinine), we obtain better result accuracy. Thus, the study

group was in favor of using the eGFR_{cys}. For populations with eGFR_{creat} < 60 ml/min/1.73 m², mortality or terminal CKD forecasting increases significantly by adding eGFR_{cys} and, especially, including the albumin/creatinine ratio. By using CKD-EPI, we can greatly improve eGFR estimates using creatinine and cystatin C. The entire issue boils down to those patients with eGFR 45-59 ml/min which do not have markers of renal injury. Cystatin C clearances, both measured and estimated, have the same difficulties in obtaining than those using creatinine. Some countries use both methods. FDA approved cystatin C dosage to measure kidney function 10 years ago.

The study group only suggests that one can measure cystatin C, since its measurement is expensive and not available in much of the world. But they insist in such measure. The data, however, is not very convincing.

PEDIATRIC CONSIDERATIONS

This discussion has no relevance in pediatrics, given that children with reduced GFR already have clear evidence of renal injury. In children, clearance discrepancies are visible only in those with high body weight.

If cystatin C is measured, it is suggested that the healthcare professional should:

- Use eGFR_{cys} more than the isolated cystatin concentration;
- Understand situations where eGFR_{cys} and eGFR_{creat-cys} are less reliable.

Clinical laboratories that measure cystatin should (1B):

- Dose it using a test with calibration referenced to international standards;
- Report the eGFR_{cys} result with serum cystatin in adults and specify the equation used whenever using eGFR_{cys} and eGFR_{creat-cys};
- Report eGFR_{cys} and eGFR_{creat-cys} in adults, using the 2012 CKD-EPI formula for cystatin C or alternative formula for cystatin C if it shows better accuracy when compared to that of 2012.

When reporting serum cystatin C results:

- Provide cystatin C concentration results rounded to the nearest hundredth of an integer, expressed in conventional units (mg/l).

When reporting on eGFR_{cys} and eGFR_{creat-cys}:

- They recommend that the results should be rounded to the nearest integer and associated with the body surface area of 1.73 m² in adults, using the ml/min/1.73 m² units;
- They recommend to report as reduced the eGFR_{cys} and eGFR_{creat-cys} lower than 60 ml/min/1.73m².

The 2012 equation using creatinine and cystatin has higher accuracy than the equations that use creatinine or cystatin alone.

PEDIATRIC CONSIDERATIONS

The following changes should be made (these assertions derive from the study of Schwartz in CkiD):

- Measure cystatin C by immunonephelometry;
- Report eGFR_{cys} together with eGFR_{creat};
- Report eGFR for children specifying the equation used.

It is suggested to measure the GFR using an exogenous marker in circumstances in which a more accurate result is required for treatment decisions. When this is necessary, it is important to know that:

- The GFR gold standard still is the test that uses inulin by continuous infusion;
- Errors in GFR measurement with exogenous markers are lower than those obtained by estimates.

FINAL REMARKS

Not all laboratories can measure cystatin. It has been considered as an alternative due to the large number of publications and their real benefits in some instances. Today, it is important but difficult to obtain the standardization of cystatin C measurements.

Estimative methods are useful when dealing with epidemiological studies.

The best equation to use depends on the region and local custom, in Europe, the USA and Australia, CKD-EPI is considered a better equation than the MDRD equation.

MANAGING CKD PROGRESSION AND COMPLICATIONS

PREVENTING CKD PROGRESSION

Chronic kidney disease (CKD) management aims to reduce a large number of elements associated

with its progression, acting on different risk factors for cardiovascular disease (CVD), when approached separately or together with specific protection measures for CKD, directly or indirectly, will have a positive impact, slowing its progress.

Hypertension (HBP) control, blocking the renin-angiotensin system (RAAS) as well as better control of some metabolic parameters such as blood glucose, dyslipidemia, uric acid and acidosis, may have an important influence in delaying CKD development.

BLOOD PRESSURE AND RAAS BLOCK

The adoption of “KDIGO Clinical Practice Guideline for the Management of Blood Pressure in CKD” is reinforced, being careful not to recommend or suggest very low blood pressure. The following are some recommendations:

- Individualize the goals of blood pressure control, as well as select agents to be used according to age, coexistence of CVD and other comorbidities, risk of progression to CKD, retinopathy (diabetic CKD) and tolerance to treatment (no rating);
- Always ask about vertigo and postural hypotension when under the use of antihypertensive drugs in the treatment of hypertension in patients with CKD (no rating);
- Individualize the treatment of hypertension in elderly patients with CKD, assessing comorbidities, other treatments, as well as the emergence of treatment-related side effects, such as electrolyte changes, abrupt worsening of renal function, postural hypotension and medication side effects;
- Treat adults with CKD, diabetic and nondiabetic patients, with a urinary albumin excretion (UAE) < 30 mg/24 h (or equivalent) with systolic blood pressure (SBP) consistently > 140 mmHg or diastolic blood pressure (DBP) > 90 mmHg, with antihypertensive drugs to maintain SBP ≤ 140 mmHg and DBP ≤ 90 mmHg (1B);
- The guidelines suggest that adult CKD patients, diabetics and nondiabetics with UAE ≥ 30 mg/24 h (or equivalent) and SBP > 130 mmHg or DBP 90 mmHg > should be treated with antihypertensive drugs to maintain SBP ≤ 130 mmHg and DBP ≤ 80 mmHg (2D);

- They also suggested to use angiotensin converting enzyme inhibitor (ACEi) or angiotensin II receptor blocker (ARB II) in diabetic adults with CKD, who had UAE between 30-300 mg/24h (2D);
- We recommend using ACEi or ARB II in diabetic adults with CKD and UAE > 300 mg/24 h; however, there is no evidence regarding the use of the association of the two classes of drugs in preventing CKD progression (1B);
- There is little evidence to recommend the combination of ACE inhibitors with ARB II to prevent CKD progression (no rating);
- It is recommended that in children with CKD, treatment for lowering blood pressure should be initiated when it is consistently above the 90th percentile for age, gender and height (1C);
- It is suggested that children with CKD, especially if they have proteinuria, should have systolic and diastolic blood pressures maintained persistently below the 50th percentile for age, gender and height, unless they develop symptoms of hypotension (2D);
- We suggest the use of ACEi or ARB II in children with CKD in which the use of antihypertensive drugs is indicated, regardless of the level of proteinuria (2D).

CKD AND THE RISK OF ACUTE KIDNEY INJURY

It is recommended that all CKD patients should be considered at high risk for developing acute kidney injury (AKI) (1A);

In CKD patients, more attention should be given when suffering from some other diseases, as well as when undergoing procedures that are known to increase the risk of AKI (no rating).

Several studies have shown a strong epidemiological association between CKD and AKI; CKD is a powerful predictor of acute decline in renal function after the use of iodinated contrast, major surgery and certain other conditions. *Diabetes mellitus*, hypertension, and proteinuria increase the likelihood of AKI development in hospitalized patients.

PROTEIN INTAKE

The role of dietary protein restriction aimed at slowing the progression of CKD is controversial, as described in a large number of reviews and meta-analyses performed in diabetic and non-diabetic patients, but in all of them, compliance with low-protein diets was very poor, it is therefore not possible to convincingly conclude that long standing protein restriction delays CKD progression.

- A protein intake of 0.8 mg/kg/day is suggested for adults with diabetes (2C) or without diabetes (2B) and GFR < 30 ml/min/1.73 m² (categories G4 and G5);
- Adult patients with CKD and at a high risk of progression should avoid higher protein intake (> 1.3 g/kg/day) in (2C).

GLUCOSE CONTROL

Diabetes mellitus is a major cause of CKD in the world and an independent risk factor for cardiovascular disease (CVD), with mortality rates that double in patients with creatinine/ albumin ratios (CAR) > 30 mg/g, which makes it important to have adequate treatment in order to prevent microvascular injury. There still are controversies as to the intensity of glycemic control to be established, with large studies showing different results, both for and against stricter glycemic control.

- It is recommended to set a hemoglobin A1c (HbA1c) target of ~ 7.0% to prevent or slow the progression of microvascular complications from diabetes, including diabetic nephropathy (1A);
- One should be very careful when trying to treat to achieve an HbA1c < 7.0% target in patients at risk of hypoglycemia and also in the interpretation of their levels in CKD patients due to decreased survival of red blood cells in this population (1B);
- The HbA1c target should be above 7.0% in individuals with comorbidities or limited life expectancy and risk of hypoglycemia (2C).

Glucose control should be part of a multifactorial intervention strategy In individuals with CKD and diabetes, addressing the control of blood pressure and cardiovascular risk by promoting the use

of ACE inhibitors or ARB II, statins and antiplatelet agents, when indicated (no rating).

SALT INTAKE

A deficiency in sodium excretion is often present in patients with CKD, causing elevation of blood pressure and proteinuria, glomerular hyperfiltration and further reduced response to the RAAS blockade. It is recommended to:

- Reduce intake to < 2 g per day of sodium (corresponding to 5g of sodium chloride) in adults, unless contraindicated i.e. in patients with salt-depleting nephropathy, postural hypotension and volume contraction without heart failure (1C);
- Sodium intake Restriction for children with CKD who have hypertension (systolic and/or diastolic > 95th percentile) or prehypertension (SBP and/or DBP > 90th percentile and < 95th percentile), based on the recommendations for daily intake per age range (1C);

Water and salt supplementation should be given to children with CKD and polyuria to prevent intravascular compartment chronic depletion and to promote proper growth.

HYPERURICEMIA

Hyperuricemia is a common finding in CKD patients, with reports of increased cardiovascular risk and CKD progression, which; however, still requires confirmation.

There is insufficient evidence to support or refute the use of serum uric acid reducing agents in CKD patients, even in symptomatic or asymptomatic hyperuricemia, with the aim of slowing CKD progression (no rating).

LIFESTYLE

It is recommended that individuals with CKD are encouraged to engage in physical activity compatible with their tolerance and cardiovascular health (in order to perform it for at least 30 minutes five times per week), reaching a healthy weight (BMI 20 to 25 kg/m², according to specific demographics of the country), and quit smoking (1D).

COMPLICATIONS ASSOCIATED WITH LOSS OF RENAL FUNCTION

CKD patients are prone to develop a variety of complications, which reflect the loss of kidney endocrine and exocrine functions. The main ones are described as follows:

- Anemia: diagnosed in CKD adults and children > 15 years of age when Hb < 13.0 g/dl in men and < 12.0 g/dl in women (no rating). In children with CKD, anemia is diagnosed if the Hb concentration is < 11.0 g/dL in children aged 0.5-5 years, < 11.5 g/dL in children aged 5-12 years, and < 12.0 g/dl in children aged 12-15 years (no rating).

In the treatment of CKD-related anemia, one should:

- Always evaluate secondary causes such as iron deficiency;
- Bear in mind that iron replacement is often effective in treating CKD anemia as initial treatment, leaving the clinician and patient to decide the route of administration (oral or IV);
- Do not use erythropoietin (EPO) in patients with active malignancy or history of recent treatment;
- Do not intentionally use EPO in the majority of patients with CKD to raise Hb above 11.5 g/dL.

CKD-MBD INCLUDING LABORATORY CHANGES

Changes in bone mineral metabolism and altered calcium and phosphorus occur early in the course of CKD and progress with declining renal function. Despite the little evidence in CKD patients who are not undergoing dialysis:

- It is recommended to measure the levels of calcium, phosphorus, PTH and alkaline phosphatase at least once in adults with GFR < 45 ml/min/1.73 m² (G3b -G5) (1C);
- Do not perform routine tests to assess bone mineral density;
- Keep normal the phosphorus values of patients with GFR < 45 ml/min/1.73 m² (G3b -G5) (2C);

- Do not routinely prescribe vitamin D supplements or its analogues in the absence of suspected or documented deficiency, or to suppress high PTH concentrations in patients with CKD who are not on dialysis (2B);
- Do not prescribe bisphosphonate treatment for patients with GFR < 30 ml/min/1.73 m² (G4-G5) (2B).

METABOLIC ACIDOSIS

The prevalence increases progressively with worsening of renal function, with detectable acidosis when GFR < 40 ml/min/1.73 m².

Chronic metabolic acidosis is associated with increased protein catabolism, uremic bone disease, muscle loss, chronic inflammation, impaired glucose homeostasis, impaired cardiac function, CKD progression and increased mortality.

- In CKD patients with serum bicarbonate values < 22 mmol/l, because of an increase in the risk of CKD progression and death, treatment should be made with bicarbonate supplementation per os, to keep normal levels, should it not be a contraindication (2B).

ACUTE KIDNEY INJURY AND CKD

We highlight acute kidney injury (AKI) as a complication of CKD that needs to be properly managed, as well as its association with progression, it is recommended that patients with CKD be considered as having an increased risk of developing AKI (1A). In fact, there are epidemiological basis for claiming that preexisting CKD predicts acute decline in renal function after exposure to radiological contrasts and major surgeries, among other medical conditions. The authors also stress the fact that there are still biomarkers capable of differentiating the “acute” from the “chronic” kidney disease in this context.

Whichever method is used to estimate GFR, hospitalization and mortality rates are higher in individuals with CKD.

REFERRAL TO EXPERTS AND MODELS OF CARE

Early identification and referral of CKD patients have the potential to revert, delay or prevent the progression of the disease, becoming the focus of the international efforts in this field and having as its goals:

1. Provide specific therapy based on the diagnosis;
2. Slow/stop CKD progression;
3. Assess and treat comorbidities;
4. Prevent and treat cardiovascular disease;
5. Identify, prevent and treat specific CKD complications (such as malnutrition, anemia, bone disease, acidosis);
6. Plan and prepare for RRT (choice of mode, access installation, preemptive transplantation, other);
7. Indicate psychological support, where appropriate, and provide conservative and palliative treatment.

It is recommended to refer CKD patients to specialist nephrology services in the following situations (1B):

1. AKI or abrupt and sustained decrease in GFR;
2. GFR < 30 ml/min/1.73 m² (stages G4 -G5);
3. Significant albuminuria (CAR > 300 mg/g, albuminuria > 300 mg/24 h, which is equivalent to approximately PCR > 500 mg/g or proteinuria > 500 mg/24 h);
4. CKD progression;
5. Maintained and not readily explained hematic cylindruria and hematuria (> 20/pc);
6. CKD and treatment-refractory hypertension with four or more antihypertensive agents;
7. Persistent changes in serum potassium;
8. Hereditary kidney disease.

In general, the determinants of referral to the specialist can vary; however, it is recommended to do so in the event of: chronic or acute reduction in renal function, severe or poorly treated hypertension, severe electrolyte disturbances, significant abnormalities in urinary tract structure, or systemic diseases with probable renal involvement; the need for education in progressive diseases, performance and interpretation of renal biopsies, or to meet the psychological stress of parents and patients.

It is recommended that individuals with CKD should be kept under multidisciplinary care (2B).

Regarding the time to start RRT, it is suggested that dialysis is initiated when one or more of the following criteria is present: symptoms or signs attributable to renal failure (serositis, acid-base and electrolyte disorders, pruritus); inability to control blood pressure or volume; progressive deterioration

of nutritional status refractory to dietary intervention, or cognitive impairment. This happens often, but not invariably with GFR between 5 and 10 ml/min/1.73 m² (2B).

It is increasingly accepted the need to provide organized care for patients who are dying or who have chosen not to do dialysis or transplantation treatment, we must provide support for these patients and their families, keeping in mind that there

is a wide range of needs for palliative treatment before death for patients with advanced CKD.

REFERENCES

This text is fully based on: “Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int (Suppl)* 2013;3:1-150.”