Chronic kidney disease: importance of early diagnosis, immediate referral and structured interdisciplinary approach to improve outcomes in patients not yet on dialysis

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Abstract

At present, chronic kidney disease (CKD) is broadly defined on the basis of changes in the glomerular filtration rate and/or the presence of parenchymal damage present for at least 3 months. Although the diagnosis of CKD is now quite straightforward, the proportion of patients with end-stage renal disease seen by a nephrologist for the first time immediately before the initiation of dialysis is still unacceptable. Early diagnosis and immediate nephrology referral are key steps in management because enable predialysis education, allow implementation of preventive measures that delay or even halt progression of CKD to end stage renal disease, as well as decrease initial morbidity and mortality. In this review, we discuss the complexity of CKD and the multiplicity of interventions currently recommended in its secondary prevention, different models of healthcare delivery, and examine the rational and outcomes of patients followed in interdisciplinary care clinics.

Keywords: chronic kidney disease, chronic kidney failure, referral and consultation, early diagnosis, glomerular filtration rate, proteinuria, interdisciplinary care model.

[J Bras Nefrol 2011;33(1): 74-87]

Introduction

Nephrology has experienced major changes since its inception in the early 1960s, when it emerged as a medical specialty. Initially, the focus of nephrology was renal replacement therapy (RRT), namely, dialysis and kidney transplantation, which became an established form of treatment for patients who had progressed to end-stage renal disease (ESRD). In Brazil during this early period, several RRT programs were created in both the public and private health systems. Nephrology in Brazil also quickly reached international levels of excellence. However, during this early period, very little attention was paid to preventive measures that preserve the glomerular filtration rate (GFR).

The last decade has revealed that the progression of chronic kidney disease (CKD) in patients with different renal pathologies who are under the nephrological care can be delayed or even halted by various measures. These include the strict control of blood pressure and the use of drugs that block the renin-angiotensin-aldosterone system (RAAS).[1] In addition, several epidemiological studies on groups of patients at risk of developing CKD, published in the last decade, have shown that the prevalence of CKD is much higher than previously thought.[1] Indeed, CKD is now considered as the great epidemic of this millennium. These observations have caught the attention of the international and the Brazilian nephrology communities, which are now starting to take various measures to manage the problem.

Epidemiology of Chronic kidney disease

CKD has received increased attention from the international scientific community since recent studies showed its high prevalence. Of particular significance is the cross-sectional analysis of the National Health and Nutrition Examination Survey (NHANES), a nationally representative sample of non-institutionalized adults aged 20 years or older, (n= 13,233) which was conducted between 1999 and 2004. CKD prevalence was determined based on persistent albuminuria (>30 mg/g)

Approved on: 01/27/2011.

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The authors declare no conflict of interest.

and decreased estimated GFR using the abbreviated Modification of Diet in Renal Disease Study (MDRD) equation reexpressed to standard serum creatinine. This analysis revealed that approximately 13% of the adult U.S. population has CKD stages 1 to 4.[2]

In Brazil, comprehensive epidemiological studies on CKD that employ the new disease definition have not yet been performed. However, a study on RRT based on data collected in January 2009 revealed that there were 77,589 patients on dialysis in Brazil, and that the prevalence and incidence of ESRD were about 405 and 144 per million population, respectively.[3] While the number of Brazilians in the different predialysis stages of CKD is not known exactly, an analysis of the laboratory data of adults that employed the new CKD definition found that 2.3% of subjects had a GFR of < 45mL/min/1.73m2 or CKD stages 3B, 4 and 5. Extrapolation of these results to the adult Brazilian population suggests that about 2.9 million Brazilians would have one third or less of GFR of normal subjects.[4]

Definition of Chronic Kidney Disease

In 2002, the Kidney Disease Outcome Quality Initiative (KDOQI) sponsored by the National Kidney Foundation published a guideline on CKD covering evaluation, classification, and stratification of risk.[1] In this important document, a new conceptual framework for diagnosis of CKD was proposed, which was worldwide accepted in the following years. The definition is based on 3 components: (1) an anatomical or structural component (markers of kidney damage), (2) a functional component (based on GFR), and (3) a temporal component.[1] based on this definition, a CKD patient is any person who, regardless of cause, has a GFR of < 60 mL/min/1.73 m^2 or a GFR of > 60 mL/min/1.73 m^2 plus at least one marker of renal parenchymal injury (*e.g.*, proteinuria), present for at least ≥ 3 months.

The KDOQI[1] also suggested that CKD should be classified into GFR-based stages, as shown in Table 1. Proteinuria (or albuminuria) represents the renal injury marker in the table since it is more frequently used, but other renal injury markers can also be employed, namely, changes in the urine (*e.g.*, glomerular hematuria), abnormal ultrasonographic images (*e.g.*, cysts in adult polycystic kidney disease), or histopathological changes seen in renal biopsies (*e.g.*, glomerular changes with or without tubulointerstitial involvement). This CKD classification system is useful because it standardizes the terminology, thereby preventing ambiguity and the overlapping of terms that are currently in use. This in turn facilitates communication between the healthcare professionals who are involved in patient care.

Optimization of Chronic Kidney Disease Patient Care

Optimal CKD management is based on three pillars: 1) early diagnosis of disease, 2) immediate referral for nephrological treatment, and 3) implementation of measures to preserve renal function.

Early diagnosis of disease

The absence of symptoms in patients in the early stages of CKD requires that clinicians maintain an adequate index of suspicion in all patients, especially in those with medical or sociodemographic risk factors for CKD. As previously mentioned, functional change, mainly in GFR, is an important component in the diagnosis and classification of CKD.

GFR is the best overall measurement of kidney function and the measure most easily understood by physicians and patients. It is defined as the kidneys' ability to clear a substance from the blood and it is expressed as the volume of blood that is completely cleared in a unit of time. Normally, the kidney filters the blood and clear the end products of protein

Table 1 CKD staging as proposed by the KDOQI[1] and updated by the National Collaborating Centre for Chronic Condition[103]

CKD stages	Glomerular filtration rate*	Proteinuria
1	≥90	Present
2	60-89	Present
3A	45-59	Present or absent
3B	30-44	
4	15-29	Present or absent
5	<15	Present or absent

*mL/min/1,73m^2.

metabolism, while preserving specific solutes, proteins (particularly albumin), and cellular components. In the majority of progressive renal diseases, the GFR falls over time as result of decrease in the total number of nephrons or reduction in GFR per nephron due to physiological and pharmacological changes in glomerular hemodynamics. GFR may be reduced even before the onset of symptoms and correlates with the severity of CKD.[1,5,6] The occurrence of increased filtration pressure or glomerular hypertrophy explains the observation of stable or near normal GFR, even when the number of nephrons is reduced. This is sometimes observed in early diabetic nephropathy, when the GFR can be increased up to 40% above of the normal value.[7]

The best, and in fact only, correct way to measure GFR is by determining the clearance of exogenous substances such as inulin, ^{125}I-iothalamate, EDTA, technetium-labeled diethylene triamine pentaacetic acid or iohexol. These agents fulfill the criteria of an ideal filtration marker, as they are excreted from the body via glomerular filtration, and suffer no further secretion and/or reabsorption when passing through the renal tubules.[8] As these substances are not present in the circulation and thus need to be infused, the measurement of these clearances is cumbersome, requires time from patient and clinical staff, and have been restricted to research purposes or to specific pathological conditions in which more simple clearance techniques offer insufficient information to guide medical decisions.

In clinical practice, the GFR is assessed by measuring substances that are normally produced by the body. Urea, the first endogenous marker used, is not completely reliable since its levels are more vulnerable to change for reasons unrelated to GFR. A high protein diet, tissue breakdown, major gastrointestinal hemorrhage and corticosteroid therapy can lead to an increase in plasma urea whereas a low protein diet and liver disease can lead to a reduction. Also, 40-50% of filtered urea may be reabsorbed by the tubules, although the proportion is reduced in advanced renal failure.[5,9]

The other endogenous marker, plasma creatinine, is the closest to an ideal endogenous substance for measuring GFR. Creatinine is almost exclusively a product of the metabolism of creatine and phosphocreatine in skeletal muscle, although ingestion of meat may also contribute slightly. Its generation is relatively constant during the day and directly proportional to muscle mass.[5,9] Creatinine is freely filtered at the glomerulus and is not reabsorbed, but up to 15% is actively secreted by the tubules. It is important to remember that non-creatinine chromogens are also detected when using the classical alkaline picrate method, which overestimates creatinine levels in the serum. The two main limitations for using creatinine as marker of GFR are: 1. As creatinine is produced in muscles, serum creatinine is dependent on muscle mass, and should be adjust for factors related to muscle mass when using it as a parameter for GFR; and 2. The inverse relation of creatinine with GFR is not a straightforward one, implying that creatinine level will rise only after the GFR has fallen to about 50-60% of its normal level.[10,11] Thus, using serum creatinine alone to estimate GFR is unsatisfactory and leads to delays in diagnosis and treatment of CKD.[1,6,10]

Clinically, the most used method for obtaining information on GFR is the 24 h urinary creatinine clearance, in which 24 h urinary creatinine excretion is divided by the serum creatinine concentration. Unfortunately, creatinine clearance does not fulfill the criteria of an ideal marker for GFR, since, as already mentioned, creatinine is excreted not only via glomerular filtration but also via secretion in the proximal tubule.[1,5,9] However, the main problem with creatinine clearance is the requirement for urine collection over 24 hours; patients find this inconvenient and, therefore, collections are often inaccurate. This is particularly so in some clinical situations (for instance, very old patients, cognitive impairment). At present, determination of GFR by creatinine clearance is recommended in extremes of age and body size, severe malnutrition, obesity, disease of skeletal muscle, paraplegia or quadriplegia, vegetarian diet, rapidly changing kidney function, and calculation for adjustment of dosage of potentially nephrotoxic drugs.[1,9]

To circumvent some of the limitations found with the determination of GFR by serum creatinine or creatinine clearance, several prediction formulas have been published. These formula use known demographic and clinical variables as surrogates for the unmeasured physiologic factors that affect serum creatinine level. The most commonly used formulas are the Cockcroft and Gault (CG),[12] MDRD,[13] and CKD-EPI equations[14] (Table 2).

The CG formula was the first of these equations to gain wide acceptance and to estimate creatinine clearance. In its original description, the CG equation was based on urinary creatinine excretion in hospitalized white males, in the age range from 18 to 92 years, and with normal renal function. It was not standardized to the body surface area of 1.73 m^2 and a correction for women was necessary.[12] It systematically

Table 2 Guidelines for the drug management of hypertension in chronic kidney disease

	Recomendation	
Organization	Diabetic kidney disease	Non diabetic kidney disease
K/DOKI	ACEI/ARB	ACEI/ARB if proteinuria is present None preferred if proteinuria is absent
BSN		ACEI/ARB
NICE	ACEI/ARB	ACEI/ARB if proteinuria or microalbuminuria is present
CARI	ACEI/ARB	ACEI/ARB
CSN		ACEI/ARB if proteinuria or microalbuminuria is present

K/DOKI: Kidney Disease Outcomes Quality Initiative;[1,37] BSN: Brazilian Society of Nephrology;[6] NICE: National Institute of Health and Clinical Excellence;[103] CARI: Caring for Australasians with Renal Impairment;[88] CSN: Canadian Society of Nephrology;[104] ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker.

overestimates GFR because tubular creatinine secretion and increase in weight due to obesity or fluid overload are not taken into account.

The MDRD study prediction equation was originally developed based on the data from the Modification of Diet in Renal Disease (MDRD) study in patients with CKD and did not include healthy individuals. The gold standard used in the development of MDRD equation was ^{125}I-iothalamate clearance, thus it predicts GFR (in mL/min/1.73 m$^{2)}$ rather than creatinine clearance.[13] In its original version, the MDRD equation required serum urea nitrogen and albumin determinations. Currently, a "four-variable" abbreviated MDRD has been advocated because it performs as well as the initial equation.[15] The GFR calculated with the MDRD equation and the true GFR are very close for results less than 60 mL/min/1.73 m^2, whereas the true GFR exceeds the estimated rate by a small amount when the GFR is greater than 60 mL/min/1.73 m^2.[16-18]

The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) group recently reported data in another large cohort including people with and without CKD to develop a newer variation of the MDRD formula.[14] The CKD-EPI equation uses the same four variables as the MDRD equation, but presents better performance and risk prediction compared with the MDRD formula. Because CKD-EPI equation has reduced bias, particularly in the higher ranges of GFR and improved accuracy, it has been recommended to replace the MDRD study equation for routine clinical use.[13]

Currently, the formulas for assessing GFR are available in programs for Palm Tops, computers and i-phones, and they are widely disseminated on the Internet (*e.g.*, on websites of the Brazilian Society of Nephrology and National Kidney Foundation). However, most professionals, particularly those working at primary care clinics, still do not have immediate access to these computer facilities and need to calculate GFR manually. This somehow tedious and time-consuming process discourages health professionals, particularly non-nephrologists, in assessing GFR routinely and thus can delay the diagnosis and nephrological referral. To circumvent this situation, we recently developed two tables, one for female and other for male, that allow health professionals to estimate GFR immediately once they know the serum creatinine level and age of a patient.[19] The tables are based on the 4-variable MDRD study formula[14] in which the black race variable (important to estimate the GFR in the U.S. black population, but with no impact among Brazilians) is deleted. The tables show the GFR values that correspond to specific serum creatinine values in the 0.5–5.0 mg/dL limits and at ages ranging from 18 to 80 years. In addition, the different CKD stages are indicated by different colors, thus facilitating the staging of CKD.[18] Although we recognize that the MDRD study equation has not yet been definitively validated in Brazil, we suggest the use of these tables at primary care level and among non-nephrologists, as a tool to facilitate the early diagnosis of CKD.

Finally, it is important to mention an upsurge of interest in cystatin C as an endogenous GFR marker. Cystatin C is a nonglycosylated basic protein with a low molecular mass (13 kD) that is part of the cystatin "superfamily" of cysteine protease inhibitors. It is produced by all nucleated cells, is freely filtered at the glomerulus and is reabsorbed and catabolized by the tubular epithelial cells; only small amounts are excreted in the urine. Consequently, although cystatin C is filtered by the glomerulus, its urinary clearance

cannot be measured, which makes the study of the factors affecting its clearance and generation difficult. Additionally, there is preliminary evidence that serum levels of cystatin C are influenced by corticosteroid use[20] and are related to age, sex, weight, height, smoking status, and the level of C-reactive protein, even after adjustment for creatinine clearance.[21]At present, the clinical role for cystatin C measurement has not been elucidated, but it may emerge as a useful marker of early kidney dysfunction as part of screening programs. Because cystatin C does not depend on muscle mass, it seems to be more sensitive than the MDRD equation in the early diagnosis of CKD,[22] particularly in older age group.[23] Additionally, it has been suggested that Cystatin C may have a role in predicting patients with CKD who have the highest risk for complications.[24]

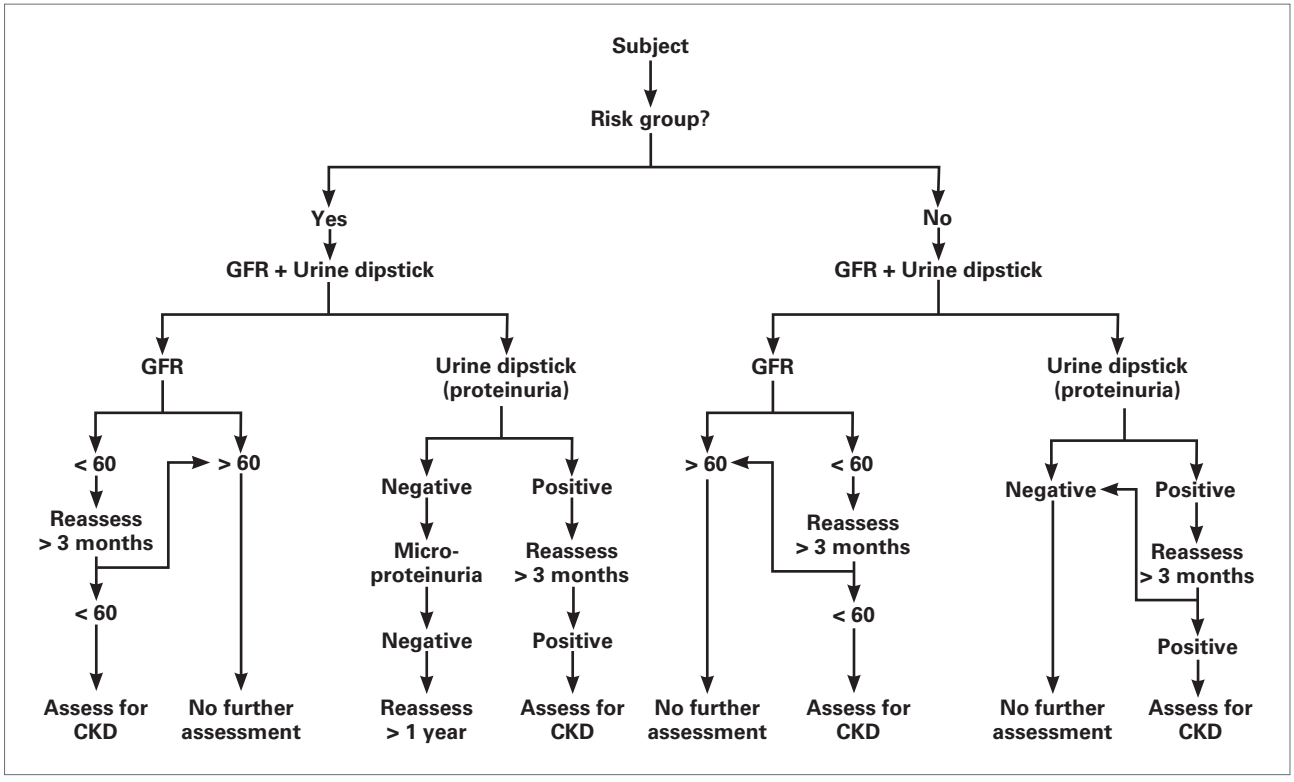
The definition of CKD is also based in the documentation of renal parenchymal injury. As mentioned above, albuminuria is the main marker of renal parenchymal injury. Albuminuria or proteinuria (albuminuria >300 mg/d) can be determined by inexpensive and easy to handle dipstick test, although it is important to recognize that the test is non-specific, semi-quantitative, and not sensitive enough to detect albumin below 300 mg/L. When proteinuria is detected, the next step is its quantification, which can be done in 24-hour urine or in a spot urine sample (in this case, the proteinuria or albuminuria concentration is divided by the urinary creatinine concentration, in order to correct for variation in urinary volume).[25] Those subjects who belong to CKD risk groups but who are negative for proteinuria in the dipstick test should be tested for microalbuminuria, using various antibody-based methods currently available (radioimmunoassay, turbidimetry, nephelometry and enzyme-linked immunosorbent assays) or a high-performance liquid chromatography (HPLC), which measures both immunoreactive and immunounreactive intact albumin.[26] In the figure, we propose a CKD screening procedure based on estimated GFR and albuminuria measurement.[27]

The urinary dipstick strip can also detect other abnormalities in the urine. For instance, a positive occult blood test may be due to hematuria and imposes confirmatory study preferably with phase contrast microcopy.[28] Other abnormalities such as bacteriuria, pyuria, and glycosuria may indicate the underlying cause of CKD.

Early referral for nephrological treatment

The second pillar of optimal CKD management is

Figure 1. Flowchart for diagnosis of chronic kidney disease.



GFR: Glomerular filtration rate in mL/min/1.73m^2; CKD: chronic kidney disease.

the immediate referral of patients to follow-up by a nephrologist or nephrology team. The literature has many examples of suboptimal CKD care provided by other medical specialists prior to referral to nephrological care. For instance, Roubicek *et al.*[29] compared CKD patients who had an early referral (ER) 16 or more weeks before the start of dialysis, and had late referral (LR) of less than 16 weeks before dialysis. It was observed that, compared to LR patients, the ER patients spent fewer days in hospital after dialysis began, were less likely to require urgent dialysis, and had better controlled blood pressure and less acute pulmonary edema. They were also more likely to start dialysis with a permanent vascular access and, therefore, less likely to need temporary central venous access. In addition, LR patients are 37% more likely than ER patients to die within the first year of dialysis.[30]

In a more recent study, McLaughlin *et al.*[31] evaluated the financial cost of managing the CKD in patients who are referred to a nephrologist either early or late. Endpoints were total cost of patient care, patient life-years, patient life-years free of RRT and hospital admission days. For the early and late referral groups, the mean total costs over five years were US$87,711 and US$110,056, respectively, the mean patient life-years were 3.53 and 3.36 years, respectively, and the patient life-years free of RRT were 2.18 and 1.76 years, respectively. In addition, patients with early nephrological follow-up spent half as long time in the hospital (25 days) as patients who were referred late (41 days). Finally, it has been shown that patients are more likely to progress to death during the first year of dialysis if they are referred late to a nephrologist.[30]

These findings highlight the importance of warning and encouraging other health professionals, especially cardiologists, endocrinologists, general practitioners, urologists and geriatricians who often handle patients at risk for CKD, to refer patients to conjoint follow-up with a nephrologist or nephrology specialist team as soon as possible. This is particularly important for cases where some functional renal impairment and heavy proteinuria are already present. The potential benefits of early referral include the identification and treatment of reversible causes of renal failure; the diagnosis and correction of factors that worsen renal function (*e.g.*, the use of nephrotoxic agents); the stabilization of the GFR; the identification and correction of major complications and of the most prevalent co-morbidities of CKD; and the achievement of better biochemical, psychological, and physical parameters at the beginning of RRT.[1,6]

Implementation of measures to preserve renal function

The third pillar of optimal CKD management is the implementation of nephroprotective measures. The course of CKD is often asymptomatic until the disease reaches its advanced stages, with the result that when the patient seeks medical attention, he or she already has one or more disease complications and/or comorbidities. At present, it remains unclear how many patients with CKD will progress to ESRD and which patients are at greater risk of needing RRT. However, it is reasonable to assume that interventions that slow or stabilize the progression of renal disease and prevent the occurrence of ESRD will have greater impact if they are implemented earlier. Furthermore, it is always important to emphasize that successful treatment of the underlying disease is also very important in preventing ESRD.

Clearly, the probability that CKD will progress is determined by complex interactions involving various clinical, environmental, and genetic factors. The main clinical factors are age, sex, diabetes, hypertension, proteinuria, anemia, metabolic complications, obesity, smoking, and dyslipidemia. For instance, the most common etiologies of nephropathy that result in CKD and ESRD have familial tendencies. Thus, it is imperative that nephrologists and primary care physicians identify those individuals who have a relative with advanced CKD, particularly those who need dialysis or renal transplantation, as these individuals are particularly prone to develop renal parenchymal diseases. Indeed, a study of incident dialysis patients showed that 20% of them reported having first or second degree relatives with ESRD, with a positive family history being more common in patients with diabetic renal disease or glomerulonephritis-associated CKD than in those with CKD associated with hypertension or other causes.[32] Thus, while the genes for kidney failure have not yet been identified, it is reasonable that family history can serve as a risk marker of future renal disease.

At present, there are effective treatments that reduce the loss of renal function and can serve in the primary prevention of CKD. For example, a study of type 2 diabetic hypertensive patients without nephropathy revealed that, compared to other antihypertensive drugs, treatment with an angiotensin-converting enzyme inhibitor over a 48 month follow-up period decreased the occurrence of microalbuminuria, a marker of CKD, by 50%.[33]

But the daily practice of the nephrologist in changing the natural course of CKD is at level of secondary prevention. It is of utmost importance that the blood pressure of CKD patients is strictly controlled, as this will minimize the disease's progression and reduce the risk of cardiovascular disease.[34] Supporting this statement is the Multiple Risk Factor Intervention Trial, which found that higher blood pressure was an independent risk factor of progression to ESRD.[35] The World Health Organization[36] and KDOQI[37] generally recommend that blood pressure values of ≤ 130/85 mmHg (≤ 140/90 mmHg in patients over 60 years of age) are optimal for patients with CKD. Table 2 summarizes the recommendations regarding blood pressure measurements and antihypertensive medications in CKD.[37]

At present, hypertension in CKD can be treated with a number of different drugs and it is not infrequent that two or more antihypertensive agents be needed to achieve optimal control of blood pressure.[38] The RAAS-blocking class of drugs has become especially important in slowing the progression of CKD, with several recent studies showing that RAAS inhibitors effectively slow the progression of diabetic[39] and non-diabetic[40] CKD.

Another important aspect of CKD progression is the occurrence of proteinuria or, more specifically, albuminuria. Initially interpreted as simply an indicator of glomerular injury, albuminuria is now considered itself to be harmful to the kidney and one of the major risk factors of CKD progression and cardiovascular diseases.[41,42,43] The degree of proteinuria correlates with the magnitude of renal injury in different animal models[44] and humans,[45] and its reduction is associated with GFR stabilization.[41] At present, RAAS blockers are preferred over other drugs for treating diabetic and non-diabetic CKD because they conciliate reduction of proteinuria with very good control of blood pressure, improvement of inflammation, and stabilization of renal function.[41,46.47]

It is not yet clear whether strict glycemic control is protective in patients with diabetic nephropathy, although it is worth to mention that, in the study by Fioretto *et al*.,[48] the achievement of euglycemia after pancreas transplantation was associated with regression of diabetic glomerulosclerosis. In any case, most authors recommend adequate glycemic control as a strategy to prevent or lessen the macro- and microvascular complications of diabetes. In particular, for both type 1[49] and type 2 diabetes,[50] intensive glycemic control has been recommended for the primary prevention of microalbuminuria and for slowing microalbuminuria progression to macroalbuminuria.

For many years, the adverse effect of obesity on kidney outcomes has been recognized in patients with primary kidney diseases in general [51] as well as in patients with hypertension and type 2 diabetes,[52] the two most common causes of CKD. Obesity may cause increased glomerular size and glomerular function abnormalities, it may also cause an unique form of focal segmental glomerulosclerosis (FSGS) with severe proteinuria, which is often accompanied by rapid loss of renal function.[53,54] Reversal of obesity improves albuminuria[55,56] and glomerular hyperfiltration in patients with morbid obesity.[57] Additionally, a study evaluating the impact of obesity on GFR revealed that obese patients subjected to unilateral nephrectomy had greater renal functional loss than non-obese patients over the 25 years of follow-up.[58]

Anemia is a common complication in patients with CKD and its treatment has been based on a large body of evidence suggesting that patients with the lowest hemoglobin values have worse outcomes than those with higher hemoglobin values. The apparent robust nature of this association, supported by known physiologic consequences of anemia (including fatigue, exercise intolerance, cognitive impairment, and cardiovascular disease exacerbation), has led most clinicians to treat anemia in CKD patients. The KDOQI guidelines recommend evaluating patients for anemia if hemoglobin (Hb) levels are < 13.5 g/dL in adult men or < 12.0 g/dL in adult women.[59] The Brazilian guidelines recommend evaluation if the Hb level is < 13 g/dL in adult men and < 12 g/dL in women and men > 65 years.[60] Both sets of guidelines recommend assessing iron stores and vitamin B12 and folate levels before considering therapy with erythropoiesis-stimulating agents (ESA). Iron stores are considered adequate if serum ferritin levels are > 100 ng/mL and the transferrin saturation (TSAT) is > 20% in pre-dialysis patients with CKD.

The use of ESA and the target level of Hb have been the subject of much research and debate. The initial clinical trials, performed in dialysis patients, ESA was given to patients who often had very low Hb levels (≤ 7 g/dL), and their anemia was partially corrected to Hb levels between 10 and 12 g/dL.[61,62] These patients experienced a dramatic improvement in their quality of life. Subsequent trials expanded the use of ESA to patients with CKD not yet on dialysis, who also often had Hb levels of 8 g/dL,[63-65] and confirmed that partial correction of anemia was reached without causing deterioration in renal function.[66,67] Several prospective clinical trials, however, have not provided definitive evidence that the treatment of anemia improves

outcomes in patients with CKD on dialysis[68] and not on dialysis.[69-71] How these important randomized controlled trials can be reconcile with those observational studies which have shown a totally different effect of Hb levels on outcomes? Although we still don't have a definitive answer to this question, it is important to realize that the health of the patient, the Hb level achieved, and the dose of ESA used are all interrelated and should be considered when treating anemia in CKD patients. In this regard, it is worth to mention the recent paper by Goodkin *et al.*72 on the effects of hemoglobin levels in hemodialysis patients maintaining naturally higher hemoglobin concentrations without transfusion or erythropoietic therapy. Compared with the other patients, those who had hemoglobin > 12 g/dL and no erythropoietic therapy presented lower unadjusted mortality risk, which was not observed after thorough adjustment for case mix (relative risk, 0.98; 95% CI 0.80 to 1.19). The authors concluded that naturally occurring Hb concentration > 12 g/dL does not associate with increased mortality among hemodialysis patients.

Based on these trials, KDOQI Initiative,[73] the European Renal Best Practice guidelines[74] and Food and Drug Administration recommend a target Hb range of 11 to 12 g/dL when prescribing ESAs. More studies are needed to assess whether Hb concentration > 12 g/dL is acceptable and safe in all CKD patients without ESA therapy.

Hyperphosphatemia directly stimulates the release of parathyroid hormone (PTH) from the parathyroid glands and inhibits 1,25-dihydroxyvitamin D synthesis, which lead to secondary hyperparathyroidism and deficiency of active vitamin D. Although vitamin D metabolism and phosphate balance are disordered in mild CKD, significant derangements usually occur only when the patient reaches the 3B and higher stages of the disease (GFR < 45 mL/min per 1.73 m^2).[75,76] The main consequence of hyperphosphatemia and vitamin D deficiency is hypocalcemia, which associates with abnormalities in bone homeostasis and with increased bone fragility and fractures, known as renal osteodystrophy.[77,78] Additionally, the imbalance of calcium-phosphorus product and vitamin D metabolism have also been linked to vascular and soft-tissue calcification, increased cardiovascular events, and death.[79-81] Although we lack evidence for long-term benefit,[82] KDOQI guidelines recommend a combination of dietary phosphorous restriction, phosphate binders, and vitamin D supplementation to maintain serum calcium, phosphorous, and intact parathyroid hormone levels within target ranges.[83]

CKD is associated with metabolic acidosis but substantial acidosis seldom occurs until the GFR is below 30 mL/min/1.73 m^2.[76] Metabolic acidosis has adverse effects on bone, nutrition, and metabolism in CKD.[84] Current guidelines recommend maintaining serum bicarbonate levels ≥ 22 mEq/L to help prevent these complications. Additionally, two recent studies in humans demonstrate that correction of metabolic acidosis with sodium bicarbonate[85] or sodium citrate[86] slow the rate of progression of CKD to ESRD. Further studies are needed to prove whether this promising and inexpensive adjunct treatment to retarding progression of CKD and improving nutritional status holds up in patients with different causes of CKD.

Finally, it is important to mention that there are other treatment approaches which effectiveness in preventing CKD progression also remains to be definitively proved. One of these is protein intake. Although restriction of protein intake may reduce the progression of diabetic and non-diabetic CKD,[87] the clinical effects are probably so small that guidelines recommend protein diets of 0.5 g/kg/day to 1.0 g/kg/day with the objective to avoid malnutrition,[88] and the daily acid[89] and phosphorus[90] loads derived from protein intake and catabolism seen as renal function decline. It is advisable that patients starting a low-protein diet be well-nourished and under the care of a dietician specialized in renal disease.

It remains unclear whether hyperlipidemia has an adverse impact on CKD progression. Likewise, the beneficial effect of statin on the GFR remains controversial. Studies using statins showed less renal functional loss in animals[91] and humans.[92] However, whereas treatment with 10 mg and 80 mg of atorvastatin was found to increase the GFR by 3.5 mL/min/1.73 m^2 and 5.2 mL/min/1.73 m^2, respectively,[93] treatment with 40 mg of pravastatin did not result in any change of the GFR.[94] Statins are as safe and secure in CKD patients as in the general population, and their possible salutary effects may be the result of lipid-dependent and lipid-independent properties. Although data are still lacking in primary prevention, lipid lowering drugs as secondary prevention seem to reduce cardiovascular mortality in patients at all stages of CKD.[95] Further studies may help to draw more precise recommendations.

Cigarette smoking is associated with accelerated progression of renal disease in patients with diabetic and non-diabetic nephropathy, along with an increased risk of cardiovascular disease.[96] Smoking has vasoconstrictor, thromboembolic, and direct effects

on the vascular endothelium and is an independent risk factor of renal failure in males with kidney diseases.[97] Smoking, along with hypertension and vascular disease, is a strong predictor of increased serum creatinine levels in non-diabetic patients aged 65 years and over.[98] Moreover, if patients with type 2 diabetes stop smoking, the risk of CKD progression is reduced by 30%.[99] Thus, while the harmful effects of smoking on CKD progression have not yet been established definitively, it is clear that this habit should be discouraged in patients with CKD.

In summary, the goals of optimal management of CKD rest on its early diagnosis, timely referral to nephrological care and treatments which slow progression of the disease and prevent cardiovascular complications. To accomplish these goals, it is important to estimate GFR and measure albuminuria regularly in those patients at risk of CKD, implement early referral of recent diagnosed cases for conjunct follow-up with nephrology specialists, and guarantee good treatment of blood pressure, proteinuria, diabetes, weight, anemia, secondary hyperparathyroidism, anemia, dyslipidemia and malnutrition.

Chronic Kidney Disease Clinical Management Models

For didactic purposes, the management of CKD can be divided into three models: 1) patients with no follow-up or with clinical non-nephrological care, 2) patients with conventional nephrological care, and 3) patients with multidisciplinary team-based care.

Unfortunately, as discussed above, it is not uncommon for CKD patients to be referred to nephrological care when they are in an advanced stage of the disease and already in need of urgent or emergent dialysis therapy. At present, there is no consensus in the literature about the optimal timing for referral to nephrological care during the course of CKD. Some authors[100,101] used 3 months prior to RRT in order to define early referral, although it seems probable that early nephrological care for 6 months would be even better, and 1 year might be ideal.[102] The minimum nephrological period before RRT is dictated by a number of factors. For example, consider the establishment of arteriovenous fistula (AVF) for hemodialysis. It is easy to imagine having to wait several days after the request before the procedure is authorized, after which the patient has to wait for an appointment with a vascular surgeon, the booking of the operating room, and, finally, the creation of the AVF. Moreover, the AVF, ideally, should not be punctured for at least 60 to 90 days. If, by chance, AVF does not develop, it will take at least another 60 to 90 days before a new fistula can be created and cannulated for the first time.

If a patient with CKD progresses to ESRD and has no access to dialysis treatment, he or she will inevitably die. However, be followed by physician does not guarantee reaching RRT with clinical parameters within the standards suggested by the CKD guidelines to prevent morbidities and mortality.[1,88,103,104] For instance, Batista *et al.*[105] retrospectively reviewed the charts of patients who were attending a specialized clinic for diabetes and hypertension. Among 146 patients who were identified with CKD, 32 (19%) were in stage 3, 40 (42%) in stage 4, and 27 (39%) in stage 5. Blood pressure control was seen in 50 (34.4%) patients, and only 65% of them were on RAAS blockers. Adequate glycemic control was seen in 65% of the diabetic patients. Registries of proteinuria and blood Hb were found in only 24% and 28% of the charts, respectively. It was not found any registry for calcium, phosphorus, sodium bicarbonate or albumin. The study shows that despite having access to physicians, a high proportion of patients with advanced CKD secondary to hypertension and/or diabetes is not receiving adequate clinical care.

Although there have been studies on the beneficial effect of early referral to nephrologist care,[106,107] standard nephrologist care *per se* is no guarantee of success in CKD management. For instance, Kausz *et al.*[108] retrospectively analyzed the records of 602 patients with CKD (defined as serum creatinine ≥ 1.5 mg/dL in women and ≥ 2.0 mg/dL in men) who were treated between October, 1994 and September, 1998 in five nephrology clinics in the Boston area, Massachusetts, United States. At the first visit, the mean serum creatinine level and GFR of the patients were 3.2 mg/dL and 22.3 mL/min/1.73m^2, respectively. Notably, even though 38% of the patients had a hematocrit of < 30%, only 18% of them were subjected to iron store studies. Moreover, of the patients with hematocrit < 30%, only 59% were treated with EPO, and of these, only 47% received iron supplementation. In addition, even though 55% of the patients exhibited changes in calcium and phosphorus metabolism, parathyroid hormone was only measured in 15% of all cases. Furthermore, the lipid profile was assessed in less than half of all patients, and only 65% of the diabetic patients (who constituted 49% of all patients) were treated with RAAS blocker. Finally, of the patients who progressed to dialysis, only 41% had AVF established before the initiation of dialysis.[108]

Another study performed in a leading nephrology center concluded that patients not yet on dialysis who received several years of standard nephrological care before commencing dialysis had a better long-term survival than those whose nephrological follow-up period was shorter.[106] It should be noted, however, that in this study, in the table that presents blood pressure and laboratory parameters, the mean Hb level of 9.5 ± 1.9 g/dL was documented even in those patients who were under nephrological follow-up for more 6 years. Such low Hb levels are suggestive of inadequate management of anemia.[73,103,104]

The third model of CKD management is based on an interdisciplinary care (IDC). It should be noted, however, that this model of care for patients with CKD is not actually new. In 1993, a National Institutes of Health-convened consensus conference proposed that patients be referred to a renal team consisting of nephrologist, dietitian, nurse, social worker, and mental health professional at some time subsequent to referral to nephrologists.[109] Despite randomized trials of IDC in other chronic disease conditions have been shown to result in improved morbidity and mortality,[110-114] to date, the studies of effectiveness of this model of care in CKD are limited and the results are uncertain.

Some 13 years ago, Levin *et al.*[115] were able to show positive impact on quantitative outcomes such as fewer urgent dialysis starts, less days in hospital in the first month of RRT and lower costs of treatment in patients cared for in an IDC compared to those followed by a nephrologist alone.

Yeoh *et al.*[116] compared 68 patients who participated in the predialysis education program with 35 patients who did not, and found that those who participated in interdisciplinary clinic had fewer emergency room visits, shorter hospitalizations and less temporary catheters used at the initiation of dialysis.

Two other studies, very similar in design, also compared patients followed in a IDC with those who had not. Curtis *et al.*[101] demonstrated significantly higher hemoglobin, albumin and calcium levels at the time of commencing dialysis in patients cared for in an interdisciplinary CKD clinic than those followed by a nephrologist alone. In the study of Goldstein *et al.*,[100] patients followed in a IDC had improved parameters in terms of albumin, hemoglobin and mineral metabolism, and more often started dialysis with a mature fistula instead of a temporary dialysis access. In both studies, it was observed that, despite equal exposure to nephrologist care after dialysis start, patients previously exposed to IDC presented improved survival.

Aiming to determine the association among IDC, survival, and risk for hospitalization, Hemmelgarn *et al.*[117] followed for 3 years IDC and non-IDC elderly outpatients with CKD matched 1:1. A Cox model was used to determine the association between IDC and risk for death and hospitalization. It was found that patients followed at IDC had a significant reduction in the risk for all-cause mortality and, although not statistically significant, a trend toward a reduction in risk for all-cause and cardiovascular-specific hospitalizations.

Although other studies done in children[118] and adults[117-121] followed in a multidisciplinary clinic indicate better outcome variables and more likely to achieve K/DOQI targets at initiation of dialysis, negative results by IDC have been reported. Harris *et al.*[122] studied 437 primary-care patients with CKD with estimated creatinine clearance of < 50 mL/min who were attending an urban academic general internal medicine practice, and divided them into two groups: One group received intensive case management, administered during the first 2 years after enrollment, consisted of mandatory repeated consultations in a nephrology case management clinic staffed by two nephrologists, a renal nurse, a renal dietitian, and a social worker. The control patients received usual care. At the end of the study, the authors found no differences in renal outcomes, health services use, or mortality in the first, second, or third through fifth years after enrollment, even though, there were significantly more outpatient visits among intervention patients, mainly because of the added visits to the nephrology case management clinic. They concluded recognizing the IDC as the state-of-the-art care, although this strategy had no effect on the outcomes of care among primary-care patients with established CKD. However, it should be noted that in this study medical care was under the control of a primary care physician and the multidisciplinary clinic primarily provided education. Thus, in view of the lack of control over medical interventions, it remains possible that the failure to demonstrate any significant differences between the two models may have been due to lack of implementation of the recommendations, not the ineffectiveness of IDC itself.

Why interdisciplinary management yields better outcomes in CKD management than conventional nephrological care is not fully understood. IDC makes sense and its basic premise is that patients with complex and multifaceted diseases such as CKD need focused and specialized care delivered from different health professionals. Thus, dietary counseling regarding salt and protein intake, ensuring medication

compliance, aid in paperwork to obtain free special medications (EPO and calcitriol), advise on weight and on quitting smoking, minimization of absenteeism in the clinic, psychological support, improving blood pressure control and greater use of renoprotective and cardioprotective medications, optimization of blood sugar control, anemia and mineral metabolism management, correction of acid-basic balance, electively planned catheter insertion or functioning fistula and timely dialysis initiation, incentive to preemptive transplantation, maintenance of oral health, exercise rehabilitation program, easier access to other specialists (urologists, vascular surgeons, cardiologists, gynecologists) are more easily and effectively implemented when these time-consuming tasks are shared by nephrologists and renal nurses and dieticians, social workers, psychologists, and, in some programs, pharmacists, dentist, and physical education professional. Although it is difficult to identify which interventions in the IDC improve patient outcomes, its structured follow-up, interactions between the core members, and prompt implementation of previously planned interventions, might be, in part, the explanation.

Conclusions

CKD is a problem of great clinical relevance, and is recognized as a complex disease demanding multiple facets in its management. Despite the translation of evidence-based medicine into daily practice has resulted in significant advances in the treatment of CKD, it is still obvious that better preparation of patients starting RRT is needed, and mortality and hospitalization have to decrease. Early diagnosis, immediate referral, and institution of measures to slow/halt CKD progression are among the key strategies to improve patients' outcomes. The sad observation, however, is that chance of death overcomes RRT as CKD progresses, even when patients have standard medical care. IDC model by offering a comprehensive organized care seems to be the best way to manage CKD, though more studies are advisable.

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