World Kidney Day 2011
Albuminuria and creatinine: simple, inexpensive and essential tests in the course of chronic kidney disease

Chronic kidney disease (CKD), contrary to what was thought not long ago, is a common disease, and is currently considered a public health problem.[1] This knowledge was possible due to the new definition that facilitated the diagnosis of CKD, mainly in its early stages, when it is frequently asymptomatic. Furthermore, early diagnosis and treatment of CKD allow to implement interventions that reduce cardiovascular morbidity, the main cause of death in CKD patients worldwide. In fact, the relationship between CKD and CVD is really well known, one favoring the development and complicating the progression of the other.[2] In both conditions, prevention through early diagnosis and the adoption of a healthy lifestyle constitute the first interventions to be taken.

It is worth emphasize that CKD is frequently silent in its early stages, so the patient may have no signs or symptoms that alert for its presence, what delays its diagnosis, postpones treatment, and favors unwanted outcomes. Particularly in its early stage, CKD can easily be identified through widely available and inexpensive laboratory tests, what allows to slow the progression to renal replacement therapy (RRT), identification and treatment of the most common complications, and prevention of early death.[3]

The measurements of serum creatinine, frequently used to estimate glomerular filtration rate (eGFR), and "micro" or "macro" albuminuria (the latter also denominated proteinuria) are tests of paramount importance for the diagnosis of CKD. In fact, the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) and Kidney Disease: Improving Global Outcomes (KDIGO) consensus meeting held in 2009, in London, UK[4] endorsed the conceptional definition of CKD previously proposed by the NKF-KDOQI[5] which defined CKD as any impairment of kidney function as evidenced by decreased GFR or other evidence of kidney damage, the latter including proteinuria, hematuria, abnormal kidney biopsy, or abnormal kidney imaging study present for 3 or more months. This definition is the basis of the current staging[4,5] of CKD and was responsible for the increased attention to the disease in clinical practice, research and public health.

Plasma or serum creatinine is considered a good marker of changes in GFR in a certain patient, however, it underperforms in measuring absolute GFR.[6] The major problems with creatinine are the analytical interference of non-creatinine chromogenes, its inverse relation with GFR, and its dependency on muscle mass. Moreover, serum creatinine increases with the ingestion of cooked meat, regardless of changes of renal function, a reason why it should be measured after 12 hours of a meat-free diet. The calculation of eGFR by MDRD[7] and CKD-EPI[8] equations derived from serum creatinine, age, gender, and race, which essentially correct for muscle mass, is now wildly recommended. If muscle mass markedly differs from the mean for age, race, and gender, eGFR will provide less reliable results, such as those calculated in amputee and undernourished patients.[5] For such patients, the recommendation is to determine the creatinine clearance in a urine sample collected over 24 hours.[5] The eGFR has been validated in individuals of different races, Brazilian included.[9] The use of eGFR is also not recommended in children, pregnant women, elderly, and at both extremes of weight.[5]

The eGFR by the MDRD equation is not sufficiently accurate for values over 60 mL/min/1.73m^2, and the current recommendation is that laboratories which already estimate renal function when measuring serum creatinine do not mention results above that value. In this setting, the CKD-EPI equation has been recommended.[8] It is important to remember that eGFR reflects GFR only in the steady state, and is not recommended to estimate the renal function of patients with acute kidney failure, a clinical situation where creatinine clearance is more appropriate.[5] The identification of reduced eGFR requires repeat the measurement after three months, aiming to confirm or not the chronicity of impairment of kidney function, or presence or absence of CKD.[5]

Screening for proteinuria can be done by detecting urinary total protein as well as its fraction, albumin. The dipstick test, widely used for screening of proteinuria, is practical, but its performance depends on urine flow. Creatinine is excreted in the urine at a relatively constant rate and can be used for quantifying proteinuria (protein/creatinine ratio or PCR) or albuminuria (albumin/creatinine ratio or ACR) in spot urine sample. Besides its convenience, proteinuria determined in spot urine sample presents excellent correlation with measurements in 24 hours urine samples.[10] -

The ACR plays a central role in diabetic kidney disease (DKD) and should be used, at least annually, for both screening kidney injury and follow-up of patients with established DKD. In non-diabetic patients, however, the role played by ACR or PCR is yet to be established, because of the controversial recommendations of the guidelines.[5,11,12]

Most studies about outcomes and interventions are based on the determination of total proteinuria, and, less frequently, on albuminuria, which is more expensive. The Coomassie brilliant blue R-250 staining to detect microalbuminuria[13] has been recently reported as a method with excellent sensitivity and low cost (each test costs about five cents of Real), what would allow its use in detecting renal parenchymal injury in the early stages of CKD.

It is worth noting that the classification of CKD into stages, currently adopted worldwide, is based on eGFR and presence of albuminuria (proteinuria).[4,5,12] (Chart 1)

Chart 1 Relationship of albuminuria and glomerular filtration in chronic kidney disease diagnosis and staging

	Estimate glomerular filtration (mL/min/1.73m2) (chronic kidney disease stage)					
Albuminuria	> 90 (1)	60-90 (2)	45-60 (3A)	30-45 (3B)	15-29 (4)	< 15 (1)
Absent (< 30 mg/day)	CKD (-)	CKD (-)	CKD (+)	CKD (+)	CKD (+)	CKD (+)
Microalbuminuria (30-300 mg/day)	CKD (+)	CKD (+)	CKD (+)	CKD (+)	CKD (+)	CKD (+)
Gross albuminuria or proteinuria (> 300 mg/day)	CKD (+)	CKD (+)	CKD (+)	CKD (+)	CKD (+)	CKD (+)

Chart 2 Relevance of estimated glomerular filtration rate and of albuminuria in the course of chronic kidney disease (CKD)

1. CKD screening and diagnostic confirmation
2. CKD staging
3. Marker of unfavorable outcomes
4. Prevention of medical error (drug nephrotoxicity)

But the determinations of eGFR and albuminuria, beside of being key in the diagnosis and staging of CKD, are also important in predicting outcomes. (Chart 2). The benefits of assessing kidney function based on eGFR are not limited to predicting which patients, over the course of the disease, will need RRT, but also include the identification of those at increased risk for accelerated loss of kidney function associated with morbidity and mortality. The lower the GFR, the more likely the need for dialysis or renal transplantation. Epidemiological studies have evidenced that the risk of a stage 1 or 2 CKD patient requiring renal replacement therapy (RRT) is lower than that of a stage 3 or 4 CKD patient, because the time required to exhaust the renal functional reserve of the former is longer. These observations, however, are not absolute, because the rate of progression of the kidney disease depends on several determinants, such as patient's age, CKD etiology, presence of risk factors associated with progression, and comorbidities, particularly those of cardiovascular origins. Naturally, the higher the amount of data about eGFR available and longer the study, more reliable the calculation of eGFR fall will be.[10,14,15] Unfortunately, so far, only a few studies have assessed the risk factors determining accelerated kidney function loss. Such studies should ideally provide data of sequential follow-up for assessing changes in eGFR over time.

So far, it is not yet clear whether the best predictor of progressive CKD is the severity of the loss of filtration capacity (expressed as eGFR) or the presence of markers of renal parenchymal lesion (expressed by albuminuria). Usually, the incidence of CKD increases as baseline eGFR worsens.[16] However, the CKD course can be different, depending on the presence of any evidence of renal parenchymal lesion. In fact, the incidence of CKD is approximately one hundred times greater in a patient with proteinuria than in another patient with the same eGFR, but with no proteinuria. In a population-based study carried out in Japan, the authors reported that a stage 1 or 2 CKD patient with proteinuria detected by dipstick had a higher risk of requiring RRT than a stage 3, and even stage 4 CKD patient with a negative test.[17] More recent data originated from the Multiple Risk Factor Intervention Trial (MRFIT) have confirmed those observations. The risk of a stage 3 CKD patient without proteinuria requiring RRT is only 2.4 times greater than that of the population with no CKD, but it is 33 times greater if the same patient has proteinuria. It is worth noting that the risk of progression to end stage renal failure (ESRF) is approximately 12 times increased for a stage 1 or 2 CKD patient with proteinuria, that is, greater than that observed in a stage 3 patient without proteinuria.[18]

In the Prevention of Renal and Vascular Endstage Disease (PREVEND) study, prospectively conducted in the Dutch population, the participants were sequentially assessed every three to four years over 6.2 years.[20] In a cohort of 6,879 participants, the eGFR was observed to decrease at a rate of 0.45 ± 1.60 mL/min/1.73m^2 per year. When adjusted for age and sex, the eGFR decrease was gradually accentuated with the increase in proteinuria.[19] At any CKD stage, the rate of decline in eGFR was greater in patients with proteinuria than in patients without proteinuria. The study also identified high blood pressure, hyperglycemia, and albuminuria as independent risk factors for progression to ESRF in both sexes.[20]

By the end of the last century, it was evident that being a CKD patient on dialysis was a predisposing factor for increased likelihood of death due to CVD. For example, the likelihood of death of a 20-year-old patient on RRT is 500 times greater than that of a healthy individual of the same age, and is about the same of an 80-year-old patient.[21] However, the association of CKD with cardiovascular mortality is not limited to dialysis patients, and can be observed in patients at the pre-dialysis stages of the disease. It is extremely disturbing to know that the reduction of eGFR gradually associates with higher mortality (mainly due to CVD) and that a patient with stage 4 CKD has twice the chance of death than begin dialysis treatment.[22] However, it is possible that other markers beside the decline of eGFR associate with higher mortality in CKD. For example, the adjusted mortality rate of a CKD patient in stage 1 or 2 (eGFR > 60 mL/min/1.73m^2) and albuminuria is twice that of a CKD patient in stage 3A (eGFR of 45-59 mL/min/1.73m^2) without albuminuria.[23]

Currently, increased levels of albuminuria[24] and decreased eGFR[25] are accepted as risk factors for cardiovascular mortality independent from the so-called "traditional" risk factors. However, the reliability of those two markers for predicting cardiovascular events is not fully settled. For example, studies carried out in Holland[26] and in the United States[27] have reported a significant increase in the occurrence of cardiovascular events in patients with CKD stage 3B (or eGFR < 45 mL/min/1.73m^2) without proteinuria. On the other hand, in a study with patients after myocardial infarction[28] and in two other population-based studies,[29,30] the risk of cardiovascular events adjusted for age and sex was not statistically elevated in patients with stage 3 CKD and without proteinuria, although it was clearly increased in those who had proteinuria.

In our study of outpatients with heart failure (HF) stages B and C, CKD stages 3 to 5 was diagnosed in 50% of the cases. After 12 months of follow up, death or hospitalization due to cardiac decompensation occurred respectively in 100% and 65% of patients with HF stages B and C if the patient presented CKD at baseline.[31] After adjusting for other prognostic factors for HF at baseline, it was observed that CKD independently increased by 3.6 times the likelihood of unfavorable outcomes.

Interestingly, the results of the studies mentioned above regarding the occurrence of increased risk for CVD in patients with CKD stage 1 or 2 compared with individuals without kidney disease are very similar to the observed relation between CKD with progression to RRT. The parallel between the impact of albuminuria as an independent predictor

of cardiovascular and renal diseases is impressive. Until recently, macroalbuminuria was considered to be only a mark of glomerular injury, while microalbuminuria indicated the occurrence of vascular injury and was not always related to renal impairment. Thus macroalbuminuria was considered a predictor of CKD, while microalbuminuria was used as a risk factor for CV events. Nowadays, however, it is evident that macroalbuminuria also associates with cardiovascular outcomes,[32,33] and microalbuminuria identifies patients with CKD and predicts those who will progress to RRT in diabetes[34,35] or hipertensives,[36] or in the general population.[19,20,29]

In conclusion, estimated GFR from plasma creatinine and measurement of microalbuminuria or macroalbuminuria (proteinuria) are simple, widely available, and high relevant clinical tests. They should be regularly performed in patients at the risk of CKD (diabetics, hypertensives, elderly, relatives on RRT), particularly in the pre-clinical stages of the disease (when eGFR is greater than 60 mL/min/1.73m^2), as well as in patients with CVD. They are interactive tests and when used together, constitute a powerful propedeutic tool in the diagnosis and prognosis of CKD, and predictors of adverse outcome including mortality.

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