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New methods for estimating glomerular filtration rate. Achieving more precision in diagnosing chronic kidney disease

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The system for classifying stages of chronic kidney disease (CKD) proposed by the KDOQI in 2002[1] revolutionised clinical nephrology by enabling practitioners to unify criteria and compare results from clinical trials and population-based studies. Thanks to this classification system, we know that CKD is very prevalent (according to data from the EPIRCE study, the prevalence of CKD in the Spanish population is 9.17%)[2] and carries high vascular morbidity.

In addition, it enabled us to confirm the close relationship between cardiovascular disease and CKD, which is more than just a coincidence due to their having common risk and progression factors. In fact, clinical practice guidelines and recent consensus documents, as well as guidelines on the management and treatment of patients with high blood pressure, recognise that both decreased glomerular filtration rate (GFR) and albuminuria are important cardiovascular risk factors.[3-5]

Incorporating the CKD stages into clinical practice and the need to identify these patients has turned up two significant weaknesses:

- The inaccuracy of GFR estimation methods.
- The fact that it is inappropriate to base decision-making solely on the GFR measurement and ignore factors such as albuminuria, which are of great prognostic importance.

GFR measurement is the best index for evaluating renal function. There are several ways to measure GFR accurately (inulin clearance, iothalamate, iohexol) although these techniques are complicated. For that reason, estimating GFR using formulas based on serum creatinine is recommended for clinical practice.

In 2006, the Spanish society of clinical biochemistry and molecular pathology (SEQC) and the Spanish Society of Nephrology (SEN) published a consensus document which recommended using the MDRD-4 or MDRD-IDMS formula depending on whether the method for measuring creatinine was traceable with respect to the reference method, isotope-dilution mass spectrometry (IDMS). This recommendation was also issued by other medical societies. The same document listed the limitations of these formulas, particularly with regard to serum creatinine, and firmly stated that it was necessary to standardise creatinine measurement by using the IDMS method in this case.[6] One of the main limitations of estimating GFR using the MDRD method is its low correlation with true GFR where values are higher than 60ml/min/1.73m^2. Laboratory reports therefore establish the qualitative value of > 60ml/min/1.73m^2 as the normal range.

Generalising the use of GFR-MDRD has led to considerable criticism being voiced, most of which is based on two reasons. Firstly it increases the number of older patients being referred to nephrology divisions despite their having little risk of kidney disease progression and little chance of benefiting from specialist care.[7] Secondly, it classifies individuals with a GFR near 60ml/min/1.73m^2, whose true renal function may be underestimated, as having kidney disease without any other data suggesting a renal condition. This can lead to administering drugs in insufficient doses, limiting use of diagnostic tests (those using iodine contrasts, or magnetic resonance angiography) and treatments (chemotherapy) and treating other vascular risk factors in an aggressive and unnecessary way.

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This is the reason why other formulas have recently been designed which estimate GFR more adequately and precisely. The creator of the MDRD equation, Dr Levey of CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) at the National Institute of Diabetes and Digestive and Kidney Disease (NIDDK), recently published a new equation, the CKD-EPI. This more precise equation, which has been validated in for the United States population, is based on standardised creatinine measurement and uses the same parameters as the MDRD (sex, race and age).[8].

The study by Montañés et al., also published in this issue of *Nefrología*,[9] compares the CKD-EPI formula with IDMS-MDRD in a cohort of 14,427 adults in the Barcelona metropolitan area. The study shows that the mean GFR estimated by CKD-EPI is higher than that obtained by MDRD- IDMS. This allows us to reclassify a large number of individuals, particularly young women, in CKD stages with a higher GFR. In this way, 9.8% of the cases categorised as 3B CKD (estimated GFR between 30 and 45ml/min/1.73m^2) would be changed to stage 3A CKD (estimated GFR between 45 and 60ml/min/1.73m^2) and 17% of those with stage 3A would be moved to stage 2 CKD. While the study does not include a comparison with methods for directly measuring GFR, and therefore cannot define the most precise formula, its results are very similar to those described by Levey et al. in the United States in that they involve reassigning individuals to more favourable stages of CKD,[8] and the authors feel that their results can be extrapolated to other populations. Therefore, in our area, this formula would be more precise for estimating GFR and more useful for precisely categorising patients with CKD, thereby preventing a large number of individuals, especially women, from being diagnosed with stage 3 CKD and receiving inappropriate treatment or referrals.

This study has its limitations, since it does not compare findings with an exact method for determining GFR and it does not describe its study population's characteristics, including race, weight or clinical context, all of which are important when we interpret results from GFR estimation formulas. However, it represents the first approximation of this new formula in a Spanish cohort, and opens the way to other studies that would be able to confirm any advantages the formula may have over other formulas currently in use.

The CKD-EPI formula is being analysed by other groups in several clinical contexts. A retrospective study in the AusDiab cohort, including 11,247 adults representing the Australian population had a similar design to that of Montañes et al. and also analysed total mortality. Using the new formula, the CKD prevalence was 11.5%, compared with 13.4% as shown by MDRD. A total of 266 patients diagnosed with CKD due to having an estimated GFR < 60ml/min/1.73m^2 had a higher GFR according to the CKD-EPI formula, and would not have been diagnosed with CKD. This group of "reclassified" individuals was at low vascular risk and did not have a higher mortality rate than the group with MDRD scores > 60ml/min/1.73m^2 (HR: 1.01; 95% CI: 0.62-1.97).[10]

In a Canadian cohort of 207 kidney transplant patients that compared GFR estimates to ^{99}mTC-diethylenetriamine penta acetate clearance as a real GFR measurement, the CKD-EPI formula was better than MDRD, especially for GFRs higher than 60ml/min. For these scores, precision (defined as variation of less than 30% with respect to the true GFR) was 89% for the CKD-EPI formula and only 77% for the MDRD formula. The authors conclude that this formula should be used instead of MDRD in transplant patients at the very least, even though its precision is still suboptimal.[11]

Another recent series that analysed different formulas in 219 patients undergoing nephrectomy used ^{125}I-Na iothalamate clearance as the GFR measurement of reference. The CKD-EPI formula was shown to have better precision (correlation of 0.86) and concordance (0.85) with the true GFR measurement. Furthermore, the rate of erroneous placements of patients in more severe CKD stages decreased by 42%.[12]

Last of all, in 101 patients with adult polycystic disease whose GFR was measured with ^{51}Cr-EDTA clearance, the CKD-EPI formula had a precision of 90%, compared with 83% for the MDRD formula.[13]

All these studies suggest that the new CKD-EPI formula is better for renal function estimates. If these first impressions are confirmed, it will replace the MDRD method in laboratory reports, provided that a standardised method for measuring serum creatinine is used, whether by traceability to the IDMS method of reference, or by using other validated standardisation methods, such as the Roche enzymatic method.[8]

However, we must always be conscious of the fact that these formulas are estimates and they should always be interpreted with reference to each patient's clinical state. Making decisions based solely on the estimated GFR measurement has many drawbacks, as we will discuss below.

Firstly, CKD as a concept implies a chronic condition, so all GFR estimates must be confirmed before an individual is diagnosed with a chronic disease. Not doing so increases risks arising from drug underdoses or from the overuse of treatment intended to decrease non-existent vascular risks. Many circumstances, such as laboratory errors, states of volume depletion or haemodynamic instability or taking certain drugs, may give rise to a temporary decrease in estimated GFR. Furthermore, when diagnosing CKD it is necessary not only to estimate GFR, but also to measure albuminuria. Apart from being an important vascular risk factor, albuminuria is the main marker of kidney disease

progression. Therefore, the following recommendation should be considered in most clinical contexts: *"If you ask for a serum creatinine measurement to estimate kidney function, ask for the albumin/creatinine ratio in a simple urine sample as well."*

Secondly, a number of clinical situations exist in which direct GFR measurements should be used instead of formulas. Dr. Levey himself, the author of the CKD-EPI and MDRD formulas, states this in a recent review in which he lists circumstances (relating to race, anthropometrics and clinical profile), listed in Table 1, under which the true GFR must be calculated precisely, using methods that are not based on serum creatinine.[14]

The current CKD classification was published in 2002, and since then it has provided a sizeable amount of information on CKD incidence, prevalence and comorbidity. However, its need for revision has also become apparent. The growing consensus is that by using current criteria, CKD diagnosis is being overestimated, which leads to inefficient use of specialist care resources. Meanwhile, using the term "chronic kidney disease" without alluding to that disease's aetiology is problematic, since it has clear prognostic implications. Furthermore, it is not clear that stages 1 and 2 without frank proteinuria, or stage 3 in elderly patients with no other alterations, are severe enough conditions to be labelled as "disease".

KDIGO and KDOQI are working together to review the current classification system, and feel that analysing **CKD patient prognosis** is the best strategy for verifying the validity of the current classification system and defining the changes that are likely to be made to this system.[15]

Meanwhile, we must continue to improve all procedures that allow us to estimate GFR more precisely, whether they entail more accurate formulas such as CKD-EPI, or the use of other biomarkers such as cystatin, which has been shown by several cohort studies to be a better predictor of mortality than formulas based on serum creatinine.[16]

Tabla 1. Indications for an exact measurement of glomerular filtration rate

- Significant changes in muscle mass (amputations, loss of muscle mass, muscular disease, paraplegia, quadriplegia)
- Extreme changes in body mass index
- Evaluation of potential kidney donors
- Individuals on strict vegetarian diets
- Monitoring the impact or toxicity of certain renally excreted pharmacological treatments
- Ethnic groups for which equations have not been validated

KEY CONCEPTS

1. A GFR measurement is the best index for evaluating renal function. In clinical practice, this measurement is done using formulas based on serum creatinine. The most widely recommended formulas at present are MDRD-4 or IDMS-MDRD.
2. Initial evaluation of the new GFR estimation formula CKD-EPI suggests that it is more precise than the MDRD method since it tends to underestimate GFR less, particularly for GFRs higher than 60ml/min/1.73m2. It enables better classification of CKD patients and prevents a sizeable number of patients, particularly women, from being diagnosed with CKD and receiving inappropriate treatment or referrals.
3. Using the CKD-EPI formula requires that the laboratory uses a standard serum creatinine measurement method.
4. In order for a diagnosis of CKD to be established, in addition to estimating GFR, albuminuria must also be measured because of its prognostic importance as a marker of kidney disease progression and vascular risk (this is normally done by measuring the albumin/creatinine ratio in a simple urine sample).
5. Despite the general way in which formula-based estimates of renal function have come to be used, there is a series of clinical situations in which GFR must be measured directly.
6. Knowledge gained in recent years about CKD means that it has become necessary to consider modifying our current CKD classification system.

APPENDIX

GFR calculators that use the CKD-EPI formula may be found on the following sites (last accessed: 01/03/2010).

- http://mdrd.com/
- http://www.qxmd.com/renal/Calculate-CKD-EPI-GFR.php
- http://www.hdcn.com/calc.htm
- http://www.nephromatic.com/egfr.php

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