SUMMARY OF THE TECHNOLOGICAL ASSESSMENT REPORT

Assessment of glomerular filtration rate and serum creatinine levels in the diagnosis of chronic kidney disease in adults

December 2011

Department of Medical and Surgical Procedures Assessment
This short text was validated by the HAS Board in December 2011.

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INTRODUCTION

Chronic kidney disease is a public health priority, and affects nearly 10% of the adult population in France. It is defined as gradual reduction in renal function, manifesting itself as a permanent reduction in glomerular filtration rate (GFR).

Early detection can delay or eliminate the need for cumbersome and costly renal replacement treatment.

In 2002, ANAES¹ set out guidelines for the management of chronic kidney disease. Since then, many sets of international guidelines have been published, and some of the ANAES guidelines have needed to be reviewed or clarified.

In view of this, CNAMTS [National Salaried Workers’ Health Insurance Fund] and the Ministry of Health, with the aim of improving levels of early detection of chronic kidney disease and improving clinical practice, asked HAS to provide answers to the following questions:

- What are the best equations for estimating GFR on the basis of serum creatinine: Cockcroft and Gault, MDRD or CKD-EPI?
- What are the best methods for determining serum creatinine which will allow the diagnosis of chronic kidney disease in adults to be made: colorimetric methods based on Jaffé’s reaction or the enzymatic methods?

BACKGROUND

- **Chronic kidney disease**
  
  **Definition**
  Chronic kidney disease (CKD) is defined as gradual reduction in kidney function, manifesting itself as a permanent reduction in glomerular filtration rate (GFR). It is defined by the presence for more than three months of markers of renal damage or a reduction in GFR to below 60 mL/min/1.73 m².

  **Classification**
  Several classifications have been put forward. In general, chronic kidney disease is classified into five stages of severity. Stages 1 and 2 are defined by GFR of more than 60 mL/min/1.73m², but with the presence of markers of renal damage. Stages 3 and 4 of chronic renal failure (CRF) are defined by GFR of between 15 and 59 mL/min/1.73m², and stage 5 (established kidney failure) of end-stage renal disease (ESRD) is defined by GFR of less than 15 mL/min/1.73m², and requires renal replacement therapy, renal transplantation or dialysis.

  **Diagnosis**
  Diagnosis of kidney disease involves testing for markers of renal damage and assessment of GFR. The latter can either be measured, based on the clearance of an exogenous marker which is neither secreted nor absorbed by the renal tubules, or estimated, using various equations, based on the blood creatinine level.

  **Treatment**
  Treatment has two purposes: to slow the progression of the disease to ESRD, and to prevent cardiovascular complications.

  Each stage of CRF requires specific management, from slowing progression to ESRD to renal replacement therapy (dialysis and transplantation).

- **Assessment of renal function**
  
  **Assessment of proteinuria or albuminuria**
  CKD is diagnosed using estimated GFR, in combination with testing for proteinuria or albuminuria, even if GFR is > 60 mL/min/1.73m². In practice, such testing can be done by measuring albuminuria/proteinuria using a 24-hour urine collection or from a spot urine sample, and in such cases the result is expressed as a urine albumin/creatinine or protein/creatinine ratio.

  **GFR measurement**
  
  **Using exogenous marker**
  Exogenous markers such as inulin, iohexol or radiopharmaceuticals are used. As these substances are not metabolised, secreted or reabsorbed by the renal tubules, and clearance of these substances through the kidneys is equivalent to GFR.

  GFR is only to be measured using these cumbersome techniques in clinical situations in which precise assessment of GFR is required.

  **Using endogenous marker**
  In usual clinical practice and in screening or early diagnosis, renal function is assessed using blood creatinine, using equations that enable estimation of GFR or creatinine clearance.

  In adults, there are various different equations. The most commonly used are the Cockcroft and Gault formula, MDRD, and (more recently) the CKD-EPI equation. These equations are less precise than measurement of GFR using exogenous markers. In addition, estimated GFR depends on the quality of blood creatinine
measurement techniques, for which there are two methods: enzyme-based techniques and Jaffé techniques.
ASSessment Method

The assessment method was based on the critical analysis of the data identified in the scientific literature and on the arguments put forward by healthcare professionals in a working group.

Research was initially focused on finding reliable guidelines (using the AGREE criteria) that answered the relevant questions. If a reliable guideline existed, there would be additional searches of the literature published since the date on which the guideline was published. If no reliable guideline existed, the literature search would cover a 10 year period.

Literature searches were carried out using the Pascal and Medline databases, the Cochrane Library, websites on which guidelines are published, technological assessment reports and websites of learned societies involved in the relevant areas (nephrology, biology).

Sixteen members were selected to take part in the working group (four nephrologists, four clinical pathologists, two geriatricians, one generalist physician, one radiologist, one engineer, one anaesthetist, one endocrinologist and one cardiologist). The working group was asked to give a reaction to the literature review and to provide additional information about this, and in particular about clinical practice in the French context. Before the meeting, individual questionnaires were sent to members, in order to shape the debate on areas of disagreement.

All members filled in a public interest declaration form. The declared interests were considered to be compatible with participation in the working group.
RESULTS OF THE ASSESSMENT: WHICH EQUATION SHOULD BE USED TO ESTIMATE GFR IN ADULTS, CG, MDRD OR CKD-EPI?

- Literature identified

One reliable guideline and 15 studies published since the date of publication of the guidelines were selected from the literature. The studies had to deal with an adult population, to make possible a direct comparison of the GFRs estimated by equations with a reference method and to present results in terms of bias, precision or accuracy.

- Results

The guideline selected (NICE) concludes that the MDRD equation is superior to the CG equation. The identified literature published since then has not called this conclusion into question.

Where bias is concerned, statistically significant results in a general population were provided by only one study and they were favourable to the CKD-EPI equation: 2.1 bias (1.7-2.4) mL/min/1.73m² compared with a bias of 3.4 (2.9-4.0) mL/min/1.73m² for the MDRD equation (IDMS).

From the point of view of precision, significantly different results in a general population were given by only one study and favoured the CKD-EPI equation for GFR > 60mL/min/1.73m²: the mean quadratic error of the MDRD equation was 0.248 (0.238 – 0.258) for MDRD (IDMS) and 0.213 (0.203 – 0.223) for CKD-EPI.

The results as to accuracy, a concept which takes account both of bias and of precision, were overall in favour of the CKD-EPI equation. Statistically significant results were given by only one study in a general population and for GFR > 60 mL/min/1.73m² where P30 accuracy was 84.7% (83.0 – 86.3) for MDRD versus 88% (86.9 – 89.7) for CKD-EPI.

- Conclusion from the findings in the literature

From the accuracy point of view, the CKD-EPI equation is superior to the other two equations in CKD screening and follow-up in an adult population and ought to be preferred.

- Working group opinion

“For the early diagnosis and follow-up of CKD”:

The diagnosis is not based on a serum creatinine value but on the estimate of GFR by a validated equation.

Of the different equations - CG (which reflects creatinine clearance and not GFR), MDRD and CKD-EPI - the CG equation should no longer be used because it reflects creatinine clearance and not GFR and it was established on the basis of methods of determination which are no longer used at present (uncorrected Jaffé).

No equation has currently been validated in certain populations:

- patients aged >75 years
- extreme weights and variations in muscle mass
- a diet poor in animal proteins and patients with malnutrition.

In these circumstances and/or when there is a need for an exact measurement of GFR, it may be useful to resort to measurement of GFR by an exogenous marker.

The ethnic corrective factor of the CKD-EPI equation has not been validated in France; specific corrective factors are in the course of validation.
CKD-EPI is the equation which has the best performance (bias, precision, accuracy), whatever the level of renal function. It should preferentially be used.

The result should be given in mL/min/1.73m²; the formula used must be specified.
RESULTS OF THE ASSESSMENT: WHICH METHOD OF DETERMINATION SHOULD BE USED TO DETERMINE SERUM CREATININE?

- Literature identified

Two studies which directly compared the methods of determination with a reference method and gave the analytical performance (precision (no bias) and reliability) of the different methods were selected from the literature.

This bibliography was completed by exploitation of the results of the external quality assessments scheme (EQAS) carried out by the AFSSAPS and by Pro.Bio.Qual, an association which organises EQA of medical biology analyses.

- Results of the studies

Precision (no bias) varied from -0.98 µmol/L to +12.31 µmol/L for a concentration of 305.7 µmol/L with enzymatic techniques and from -3.81 µmol/L to +12.30 µmol/L for concentrations of 305.7 µmol/L and 76 µmol/L respectively with Jaffé techniques. With these data it was not possible to distinguish between the two methods by means of the study of precision (no bias).

With the exception of the dry chemistry enzymatic method for which the authors of the study reported incorrect calibration, the reliability of the enzymatic methods was always better than for the Jaffé methods: CV < 4% versus CV > 5% for serum creatinines < 80 µmol/L, CV < 3.5% versus CV > 4.5% at 153 µmol/L and CV < 3% versus CV > 4% at 305.7 µmol/L.

- Results of the EQA scheme

On the basis of the EQAS data it was not possible to rule on the superiority of one technique over the other in terms of precision (no bias), as the value assigned to the samples resulted from the means by groups of techniques. The analysis of the data from the EQAS also showed that the enzymatic techniques were more reliable as compared with the Jaffé techniques, especially at low and normal creatinine concentrations. The differences for high serum creatinines were less.

- Conclusion from the findings in the literature

The analytical performance of the enzymatic techniques appears to be higher than that of the Jaffé techniques for low and normal serum creatinine values. This superiority is less when serum creatinine increases.

It was not possible from the data identified from the literature to specify at which blood creatinine concentrations the differences in performance are narrow enough for it to be possible to use both methods equally well and with no clinical impact.

- Working group opinion.

"Only techniques of creatinine determination which are traceable on IDMS should be used.

The analytical performance of the enzymatic methods is superior to that of the corrected Jaffé methods and it meets the recommendations of the NKDEP (precision (no bias) and reliability).

The CKD-EPI equation was established on the basis of the measurements carried out using enzymatic techniques. In the present state of knowledge, it therefore appears to be logical to recommend these techniques for the estimation of GFR."

2 In this study, an erroneous calibration of the dry chemistry enzymatic method was pointed out.
The working group emphasises the fact that, at the moment, the cost of the enzymatic reagents is higher than that of the Jaffé techniques and it also reports the data from the Pro.Bio.Qual study which show that only 18.7% of laboratories use enzymatic techniques\(^3\).

The delivery of the result should state the technique employed."

\(^3\) According to ProBioQual, the non-standardised, un-corrected Jaffé technique accounts for 18.9% of techniques used in laboratories, the uncorrected standardised Jaffé technique for 21.5% and the standardised and corrected Jaffé technique for 40.9%.
CONCLUSIONS AND FUTURE PLANS

Which equation should be used to estimate GFR in adults?

After analysing the data from the literature and consulting the experts, the HAS concludes:

For the early diagnosis and follow-up of CKD in an adult population, the diagnosis should be based on the estimate of the GFR obtained with the CKD-EPI equation, which gives the best performance in terms of accuracy.

While waiting for the health professionals to adopt this new equation, the MDRD formula may be used in the meantime.

The ethnic correction factor for the equation does not apply in France.

- The HAS cannot rule on the validation of this equation in patients:
  - aged over 75 years of age
  - with extremes of weight or considerable variations in muscle mass
  - with a diet poor in animal proteins or who are suffering from malnutrition.

The HAS draws attention to the difficulties related to calculating the dosages of drugs whose Summaries of Product Characteristics (SPC) mention an adjustment of dosages as a function of creatinine clearance estimated with the CG formula.

It would be desirable for the SPCs to be revised so that the dosages of the drugs can be adjusted in accordance with the GFR estimated by the CKD-EPI equation.

Which method should one use to determine serum creatinine?

After analysis of the data in the literature, EQAS and consultation of the experts, the HAS concludes:

To make it possible to estimate the GFR with the CKD-EPI equation, judged more efficient in the early diagnosis of CKD in adults, the determinations of serum creatinine ought to be carried out with methods traceable on IDMS.

The analytical performance of the enzymatic methods means that they can be used whatever the blood creatinine concentration is and in all clinical conditions, while at low concentrations of creatinine and those close to the clinical decision-making threshold, the analytical performance of the Jaffé methods does not always reach the acceptable limits set by the NKDEP and cannot therefore be used in every situation. It has not been possible however to define the serum creatinine threshold beyond which differences in analytical performance between methods no longer have a clinical impact.

For practical reasons and to facilitate patient follow-up, the HAS recommends enzymatic techniques in all clinical situations.

The results of a French study which is in the course of being published are eagerly awaited. Whether these results confirm these conclusions or otherwise will have to be verified.