Measurement uncertainty of creatinine in low values: Another good reason not to use the MDRD formula with low creatinine values

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Measurement uncertainty of creatinine in low values: another good reason not to use the MDRD formula with low creatinine values.

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Estimation of the glomerular filtration rate (GFR) by the MDRD (1) equation is now widely used in clinical practice. Guidelines (2) recommend that clinical laboratories compute and report estimated GFR by using such an estimating equation to facilitate detection of chronic kidney disease. However, several authors have shown that this formula should not be applied to patients with a normal renal function because it lacks accuracy and precision for GFRs over 60 ml/min/1.73 m^2 (3). All "normal" GFRs must be reported as "> 60 ml/min/1.73 m^3" without any precision of the value (4). There are many explanations for this inaccuracy: the variation of the serum creatinine assay calibration (5), the fact that the patients enrolled in the MDRD study had a renal failure and that the relationship between creatinine and GFR are not the same in normal and renal failure populations (6) and finally the precision of the Jaffé methods (7). We have recently illustrated the impact of the critical difference concept for MDRD results with normal creatinine values (8).

There is another consideration that, to our knowledge, has not been evaluated. Measurement uncertainty characterises the dispersion of the values that could reasonably be attributed to the measurand. The evaluation of the measurement uncertainty is described in the ISO document Guide to the Expression of Uncertainty in Measurement (GUM). However, the application of this guide is, in practice, very difficult (9). There are two possible evaluations of the uncertainty: type A evaluation, that can be calculated by statistical means from repeated measurements and type B, which uses prior information like reported uncertainties of a reference material, calibration certificates, resolution, instability.

In clinical biology, where we work with complex matrix like serum, we should combine both uncertainties to have a better estimation of the uncertainty with the formula $u(G) = (u^2_A(G) + u^2_B(G))^{1/2}$, where u is the uncertainty, and G the measurand. In our routine

practice, we evaluate u_A as the standard deviation of the quality controls realised on a long period of time, covering at least 3 reagent lots and all relevant instrument maintenance conditions, multiplied by a factor k (k=2 for a 95% confidence interval and k=3 for a 99% confidence interval). Type B uncertainty statement estimated and expressed according to GUM should be given by the manufacturer.

We use the compensated kinetic Jaffé method for the creatinine measurement (Modular, Roche Diagnostics, Mannheim, Germany) in our laboratory. From November 2005 to July 2006, we have performed 1800 quality controls for the creatinine test, with a mean of 0.725 mg/dl and a standard deviation of 0.035 mg/dl. We can then evaluate u^2_A with a 95% confidence interval: $(2 \text{ X } 0.035)^2 = 0.0049$ mg/dl.

The uncertainty on the C.f.a.s calibrator at 4.39 mg/dl used to calibrate our creatinine kits is 0.0760 mg/dl (Roche Diagnostics Traceability and Uncertainty document for C.f.a.s Proteins, April 2006; reference method:GC-MS). We can then evaluate u^2_B at 0.00578.

The uncertainty of creatinine for our 0.725 mg/dl control is then = $(0.0049 + 0.00578)^{1/2}$ = 0.103 mg/dl. In other words, this means that the “true” value of our measurand is comprised between 0.622 and 0.828 mg/dl. As the relationship between GFR and creatinine is exponential, small variations of creatinine induce large variations in GFR. When the two latter values are introduced into the simplified MDRD formula for a 60 years old man, the results are 140 and 101 ml/min/1.73 m², respectively. The absolute differences between these estimated GFRs and GFR estimated with 0.725 mg/dl which is 117 ml/min/1.73 m² are 23 and 17 ml/min/1.73m².

Our approach is not free from criticism. In fact, a quality control is not a sample patient and our uncertainty is not the “true” uncertainty as determined by the GUM guidelines, but rather a close evaluation of the uncertainty.

We would have certainly observed a smaller uncertainty on the high level control. Indeed, the value of this control is closer than the value of the calibrator. Now, because of the exponential relation between GFR and creatinine, it is of importance that uncertainty in the low creatinine values is the smallest possible. We are then persuaded that creatinine reagents should be calibrated with at least three points, with one point near 1 mg/dl instead of the traditional two points calibration.

Once again, our data show that one should be cautious when applying the MDRD formula to a patient with a normal renal function or for normal creatinine values.

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